PMOD Kinetic Modeling (PKIN)

USER MANUAL
Version 4.2

PMOD is a software
FOR RESEARCH USE ONLY (RUO)
and must not be used for diagnosis or treatment of patients.

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1   *PMOD Kinetic Modeling Tool (PKIN)*

The PMOD kinetic modeling tool represents a flexible environment for the simulation and fitting of models over time. While initially aimed at the compartment models employed in Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), models for other modalities such as magnetic resonance or optical imaging can also be easily incorporated due to the general approach and the plug-in structure for the models.

PKIN includes the following features:

- import of time-vectors from measurements of blood and tissue activity via text files or directly from the PMOD Volume-Of-Interest (VOI) tool,

- fitting of plasma fraction curves to derive tracer activity in plasma from whole blood activity,

- fitting of metabolite correction curves to derive free tracer activity from total plasma activity,

- representation of the plasma and whole-blood activity by a model for data smoothing and extension beyond the last measurement,

- selection of a comprehensive list of compartment models, reference models and graphical plots,

- weighted and non-weighted fitting of the selected model to the measurement whereby the parameter can be enabled or fixed, and can optionally be restricted within a physiological range,

- coupled fitting of measurements from different tissues to improve the accuracy for parameters assumed to be identical across tissues,

- calculation of goodness-of-fit criteria usable for model comparisons,

- Monte Carlo simulations to assess the identifiability of model parameters using a standard or user-defined distribution of the measurement errors,

- sensitivity analysis of compartment models to quantify the correlation between the model parameters,

- visualization of the relative contributions of the different compartments to the model curve,

- generation of synthetic studies representing compartmental kinetics for testing the performance of simplified pixel-wise models,

- batch mode operation to fit or Monte Carlo simulate a set of prepared studies,

- saving of the fitted parameters into text files and their aggregation for further statistical investigations.

Please note that the following description is intended as a reference and not as a tutorial. For practical examples how to work with the PKIN software please refer to the **PMOD Workbook**, which is distributed as part of the PMOD documentation and available online.

2   *Introduction to Modeling in PET*

For the data processing in PKIN it will be helpful to understand the basic modeling concepts in PET. The following sections present short introductions of compartment and reference models. Other model types are described in the [PKIN Model Reference](#) ⌐166⌐ section.

For in-depth understanding of PET Kinetic Modeling we strongly recommend the PMOD users to attend one of the excellent yearly *PET Pharmacokinetics Courses.* These courses include theory as well as practical work and are organized by the the top experts in the domain. The 2018 course is likely scheduled July 9 - 12, 2018, in London, prior to the [BrainPET](#) Meeting. Another worthwhile course is *PET Methodology* (King's College London). An additional source of valuable information is the [data analysis website](#) of the Turku PET Centre.

2.1   Compartment Models

A physiologic system is often described by decomposition into a number of interacting subsystems, called *compartments.* Compartments should not be understood as a physical volume, but rather as a mass of well-mixed, homogeneous material that behaves uniformly. Each compartment may exchange material with other compartments. Examples of frequently used compartments are

- Authentic (unchanged) tracer in the arterial plasma that can be extracted into the tissue. The concentration of authentic tracer as a function of time during the PET acquisition is called the "Arterial Input Function" (AIF), or simply the "Input Curve".
- Free tracer in tissue that can be bound or that may diffuse back into the blood.
- Tracer in tissue that has been specifically bound, for instance, at the target receptor site.
- Tracer in tissue that has been non-specifically bound to other than the targeted cell components.

Compartment models are visualized by diagrams wherein the rectangles symbolize compartments and the arrows represent material exchange, as illustrated for the different models below. Although the mechanisms of material transport between compartments may differ, models that can be reasonably analyzed with standard mathematical methods assume first-order processes. As a consequence, the change of tracer concentration in each compartment is a linear function of the concentrations in the other compartments. Because of the tiny amounts of tracer material applied in nuclear medicine it is usually assumed that the observed system is not disturbed by the tracer. It is furthermore assumed, that the physiologic conditions do not change during the study, so that the rate of the material exchange can be considered constant.

2.1.1   Model Structure

In the following, the compartment models are illustrated using a tracer that is injected intravenously as a bolus and is not freely diffusible. Please refer to the consensus paper of [Innis et al](#) [56] for the details of the nomenclature and the interpretation of the models in the context of brain receptor tracers.

When the tracer arrives in the heart chambers, it is well mixed with blood and distributed by the arterial circulation. It finally arrives at the capillary bed where exchange with the tissue can take place. Some fraction of the tracer is extracted into tissue and metabolized, the rest is transported back to the heart, from where a new circulation starts.

This simplified "physiologic" model can be translated into a 1-tissue compartment model (**1TCM**):
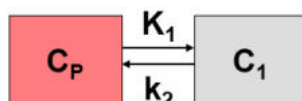
Because of mixing it is assumed that, the arterial tracer concentration is the same throughout the body, so that it can be measured in a peripheral artery. The tracer concentration in tissue $C_1(t)$

increases by the extraction of tracer from the arterial blood plasma. A usual condition for a quantitative analysis is, that only the unchanged tracer, called the *authentic tracer* or *parent*, can enter tissue, whereas labeled metabolites which may also circulate cannot. Because extraction is described by a first-order process, the transfer of material is proportional to the parent concentration $C_P(t)$. Parallel to the uptake, tracer in tissue is reduced by a backwards transfer (or washout), which is proportional to the concentration in tissue. Both processes compete, so that the change over time of the net tracer concentration in tissue ($dC_1(t)/dt$) can be expressed by the following differential equation

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t)$$

The two transfer coefficients, K_1 and k_2, have a somewhat different meaning, indicated by using capital and small letters. K_1 includes a perfusion-dependent component and has units of milliliter per minute per milliliter tissue, whereas k_2 [min^{-1}] indicates the fraction of mass transferred per unit time. For example, if k_2 equals 0.1[min^{-1}], material leaves the tissue compartment at a rate of 10% per minute. The parent concentration $C_P(t)$ is not a compartment, but considered as a measured quantity and appears as the input curve driving the system.

The differential equation of the 1-tissue compartment model can be analytically solved (integrated), yielding the following equation for the concentration of tracer in tissue:

$$C_1(t) = K_1 C_P(t) \otimes e^{-k_2 t} = K_1 \int_0^t C_P(t) e^{-k_2 (t-\tau)} d\tau$$

Hence the time course of the tissue concentration essentially results from a convolution $\otimes$ of the input curve with a decaying exponential. K_1 acts as a scaling factor of the concentration course, whereas the washout coefficient k_2 has an impact on its form.

More complex compartment models distinguish different forms of tracer in tissue, which is usually interpreted as follows. After entering a cell, the tracer is available for binding in a free form at a concentration $C_1(t)$. Free tracer can directly be bound to its target molecule, $C_2(t)$, but it also may bind to some cell components that are not known in detail, $C_3(t)$. Considering these pathways, a 3-tissue compartment model (**3TCM**) with six transfer coefficients is established, whereby C_2 and C_3 communicate only by C_1.
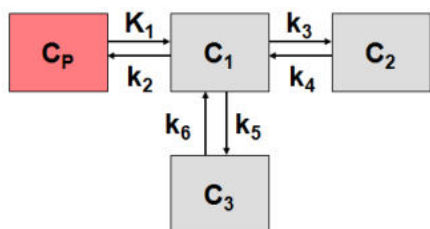
The system of differential equations can be derived in analogy to the 1-tissue compartment model, but is much more complex. The equations describing this model are given by

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3 + k_5) C_1(t) + k_4 C_2(t) + k_6 C_3(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$
$$\frac{dC_3(t)}{dt} = k_5 C_1(t) - k_6 C_3(t)$$

This system contains six unknown parameters (K_1 to k_6) that are difficult to assess experimentally. For practical purposes, the system is therefore most often reduced to a 2-tissue compartment model (**2TCM**) by treating free and non-specifically bound tracer as a single compartment C_1 (non-displaceable compartment).
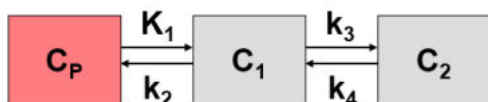
This simplification is justified if the exchange free $\leftrightarrow$ nonspecific binding is significantly faster than the exchange free $\leftrightarrow$ specific binding. Otherwise specific and nonspecific binding cannot be distinguished, and the resulting transfer coefficients cannot be attributed to specific binding alone. The simplified two-tissue compartment model is given by

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

By using a mathematical method called Laplace transformation, analytic solutions can be derived for linear multi-compartment models, but the mathematical formulas are complicated expressions already for two compartments. However, they demonstrate that generally K_1 represents a scaling factor like in the solution given for the one-tissue compartment.

Model Simplification

While complex models are a more realistic description of the involved processes, they include many parameters. PET data from dynamic measurements has a limited statistical quality, and represents the summed contributions from all compartments. When trying to estimate a large number of model parameters from such data, the variance of the resulting parameters tends to be too high for reliable interpretation. Therefore, only relatively simple models with 2 to 4 (at most 6) parameters are feasible in practice.

When the 3-tissue compartment model is simplified to a 2-tissue compartment model, and further to a 1-tissue compartment model, the meaning of the transfer coefficients changes (except for K_1). The "lumped" parameters of the simplified models can be expressed by the parameters of the complex models as shown in the tables below. Note that k_2 and k_3 have a different meaning in the different models, as well as C_1.

Parameters in 1TCM	Expressed by parameters of the 2TCM	Expressed by parameters of the 3TCM
K_1	K_1	K_1
k_2	$\dfrac{k_2}{1 + k_3/k_4}$	$\dfrac{k_2}{1 + k_3/k_4 + k_5/k_6}$

Parameters in 2TCM	Expressed by parameters of the 3TCM
K_1	K_1
k_2	$\dfrac{k_2}{1 + k_5/k_6}$
k_3	$\dfrac{k_3}{1 + k_5/k_6}$
k_4	k_4

The term $1/(1+k_5/k_6)$ represents the free fraction of tracer in the non-displaceable tissue compartment which is available for transfer back to blood or for specific binding, and is often called f_2.

A good summary on the configuration and interpretation of linear models for receptor tracers is given by Koeppe et al. [15]. Starting from the 3-tissue model it is nicely shown how the parameters of simplified models are related to the true rate constants. **PKIN** can take these relations into account when switching from a more complex model to a simpler one. This behavior can be switched on by the **Model Conversion** check on the **Extras** panel.

Relation of K1 with Perfusion

As mentioned earlier, K_1 is related to tissue perfusion F. With a capillary model, the relation

$$K_1 = EF$$

can be derived. E represents the unidirectional first-pass extraction fraction (i.e., the fraction of tracer that penetrates the capillary wall and is extracted into the tissue during the first pass of tracer through the capillary). The reverse transport is not regarded in the calculation of E. Renkin [40] and C. Crone [41] calculated the extraction as

$$E = 1 - e^{-PS/F}$$

P denotes permeability, and S, the surface of the endothelium by which the capillary exchanges with the tissue. The relation demonstrates that the extraction depends on the properties of the endothelium with respect to the tracer (PS), as well as the perfusion F. The higher the perfusion, the smaller the extraction, because the average time spent close to the capillary wall decreases. However, total mass transport in general still increases with flow, as the reduced extraction is more than compensated by the higher abundance of tracer (F in the term EF). For tracers with very high permeability, the extraction is virtually independent of perfusion and E approaches 1 (such as for ^{15}O-labeled water). In this case, K_1 equals perfusion.

Volumes of Distribution for Receptor Tracers

For receptor tracers, it is important that the extraction from plasma to tissue is sufficient, such that the kinetics is not limited by the extraction step. Additionally, the relation of the transfer coefficients for specific and nonspecific binding determines whether these different types of binding can be distinguished.

Naturally, the main interest is in specific binding. Besides the individual rate constants k_3 and k_4, which are often difficult to estimate precisely, the distribution volume of specific binding V_S is a measure which is often used to quantify specific binding. V_S is defined by the ratio of specific binding concentration to total parent at equilibrium (which may not occur during the experiment). However, it can also be calculated from the rate constants of the 3-tissue compartment model as follows.

$$V_s = K_1/k_2 * k_3/k_4 \quad \text{3-Tissue Compartment Model}$$

Under the assumption of a rapid equilibration between the free and non-specific compartment the same expression with the rate constants from the 2-tissue compartment model is often used as an approximation of V_S.

If the assumption of rapid equilibration is not justified one must resort to considering the entire tracer concentration in tissue as an indicator of specific binding. The measure used in these cases is called the "total distribution volume" V_T. In general it is defined as the ratio of the tracer concentration in tissue to total parent in plasma at equilibrium. A V_T equal to 20 hence means that the tracer is being concentrated in tissue by 20:1. V_T can be easily computed from the rate constants of the compartments model.

$$V_T = K_1/k_2 \quad \text{1-Tissue Compartment Model}$$

$$V_T = K_1/k_2 \, (1+k_3/k_4) \quad \text{2-Tissue Compartment Model}$$

K_1/k_2 can be interpreted as the distribution volume of the first tissue compartment C_1. In receptor tracer experiments, this compartment is usually called the non-displaceable compartment, and K_1/k_2 the distribution volume V_{ND} of non-displaceable uptake,

$$V_{ND} = K_1/k_2 \quad \text{2-Tissue Compartment Model}$$

This naming indicates that the concentration of free and non-specifically bound tracer in tissue is not reduced when a non-labeled ligand is brought into the tissue, competing with binding to the same receptor as the tracer. The rational for this assumption is that the potential for non-specific binding to various cell components is practically unlimited as compared to the number of specific binding sites.

Rate Constants and Binding Potential for Receptor Tracers

- k_2 represents the fractional rate constant for the washout of free tracer from tissue to plasma. It it is a composite rate constant and is related to flow in the same way as K_1. Consequently it is often reasonable to assume that the ratio K_1/k_2 is insensitive to flow and regionally constant. This property can be exploited as a restriction in a model fit, hereby reducing the number of fitted parameters.

- k_3 is regarded as the rate of association of the ligand with the specific binding sites. It is a function of the concentrations of the free radioligand, the available binding sites and intrinsic second order association rate constants. Consequently it is a pseudo first order rate constant incorporating the concentration of available binding sites.

- k_4 is considered as the dissociation rate constant of the receptor-ligand complex; often it is assumed to be invariant, what is still a matter of debate.

The binding potential (BP) quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration. Particularly, the ratio at equilibrium of specifically bound radioligand to that of non-displaceable radioligand in tissue is referring to as BP_{ND} (unitless) and equals the ratio k_3/k_4.

2.1.2 Input Curve

With rare exceptions only a fraction of the tracer in blood is exchangeable with tissue and thus needs to be determined from blood aliquots which are withdrawn from an artery during the whole study. This process is highly crucial for the quantification outcome. Please refer to our application note for a thorough discussion of all required processing steps and potential pitfalls.

A whole blood sample comprises tracer in the red blood cells and different tracer categories in the plasma: free unchanged tracer (parent), tracer bound to plasma proteins, tracer chemically changed by metabolite processes (metabolites). Depending on the tracer ligand, exchange processes are continuously going on between the different tracer pools in blood.

Blood Sample Analytics

The following blood analysis steps are required in quantitative PET studies to determine the concentration of unchanged tracer in plasma as the Arterial Input Function (AIF).

1. Separation of the plasma from the red blood cells by centrifugation.
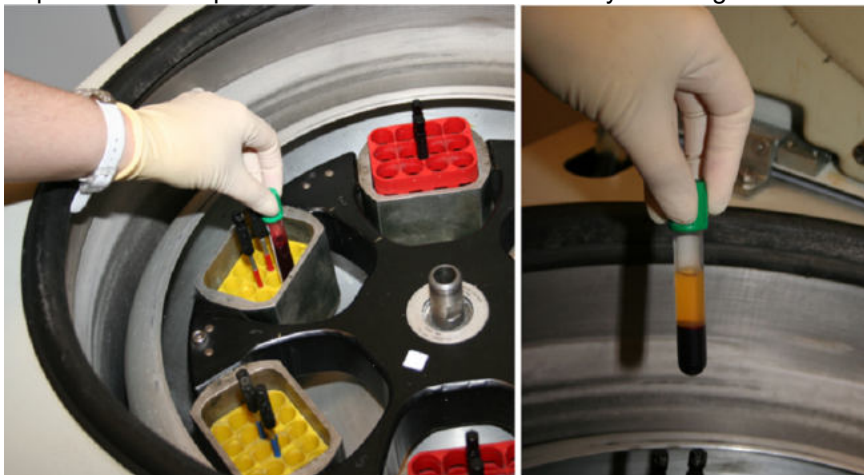
Plasma represents about 60% of the total blood volume.

2. Further separation of tracer in plasma into tracer metabolites and unchanged tracer by filtration

or HPLC (High Performance Liquid Chromatography).
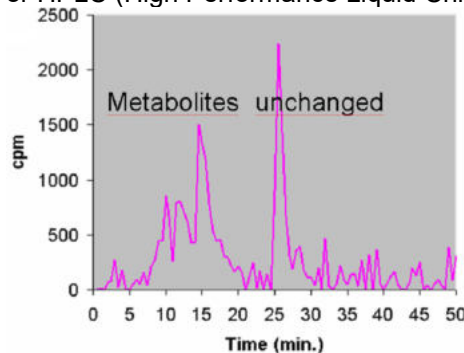
3. Determination of the free fraction of unchanged tracer in plasma (f_p), i.e. the fraction of tracer not bound to plasma proteins. Often f_p is difficult to measure and thus not explicitly used. Hereby, $f_p = 1$ is assumed, and the unchanged tracer concentration is regarded as the input function.

After the different tracer fractions in blood have been separated, it is necessary to calculate their activity concentrations. This is done by measuring them in a radioactivity counter and dividing the activity by the fractional volumes.

Fitting of Blood Curves by Models

Due to the experimental procedures involved the blood activity measurements are typically noisy and contribute a considerable amount of uncertainty to the analysis. Therefore it is often reasonable to fit analytical functions to the blood-related measurements, which is also applied for the interpolation between the samples, as well as for the extrapolation at late times when blood samples might be lacking.

The example below illustrates the blood model approach.

• The black triangles represent the activity of tracer (free, bound to proteins, metabolites) in the arterial plasma during the study. A tri-exponential function which was fitted to these measurements and shown as the black line.

• The green circle represents the measurements of the fraction "Unchanged tracer in plasma" to "Total tracer in plasma". A model was fitted to these fraction values and shown as the green line.

• The arterial input function (AIF) is obtained by the multiplication of the two model functions and represented by the red curve, implicitly assuming $f_p = 1$.

Note the sharp concentration changes at the early times after injection. To capture these changes adequately, rapid blood sampling is required during the first minutes after tracer injection.
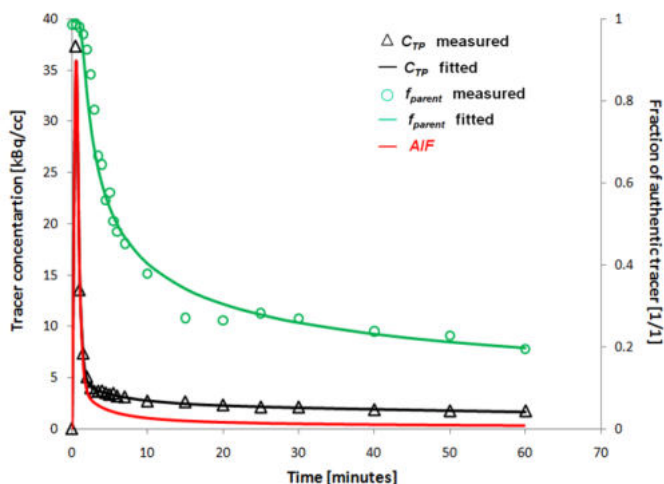
2.1.3 Calculation of the Model Curve

The signal of a dynamic PET measurement represents the averaged activity in the image pixels at acquisition times *t* starting at tracer injection. It is described by the **operational equation**

$$C_{Model}(t) = (1 - vB)\, C_{Tissue}(t) + vB\, C_{Blood}(t) \cong C_{PET}(t)$$

This equation means that the activity concentration C_{PET} measured by PET in a certain tissue volume is composed of two contributions:

- tracer which has been extracted into tissue, where it has an instantaneous concentration of $C_{Tissue}(t)$.

- tracer which is circulating within the blood, with a concentration $C_{Blood}(t)$.

Hereby it is assumed, that the fractional volume vB is composed of small capillaries (2%-5%) filled with whole blood, and that the fraction (1-vB) represents tissue. The blood activity C_{Blood} must be measured during the acquisition. In tissue, the tracer may be present in different spaces or forms (eg. *free*, *specifically bound, non-specifically bound*), which are described by the compartments of the model. All compartments contribute to the tissue signal, so that it is modeled by the expression

$$C_{Tissue}(t_k) = \sum_i \frac{1}{(t_k^{end} - t_k^{begin})} \int_{t_k\,begin}^{t_k\,end} C_i(t)\,dt$$

whereby

- $C_{Tissue}(t_k)$ represents the average concentration of tracer in tissue during the acquisition *k* which starts at t_k^{begin} and and lasts until t_k^{end}

- $C_i(t)$ represents tracer concentration in compartment *i* at time *t* . These expected concentrations are calculated from the differential equations using the current model parameters and the plasma input curve(s).

The operational equations used for other than compartment models are specified in the PKIN Model Reference section [117].

2.1.4 Fitting and Residual Weighting

Least Squares Optimization

The fitting methods available optimize the agreement between the measurements and the model curve. Effectively, they minimize the difference between them, whereby the difference is described by the Chi Squares criterion (cost function) below:

$$\chi^2 = \sum_i w_i \left[C_{PET}(t_i) - C_{Model}(t_i) \right]^2$$

This expression implies that the squared residuals (measured value minus estimated model value) are multiplied by weights. To satisfy the requirements of *least squares* fitting, the weights w_i should be related to the variance σ_i^2 of the measurements by

$$w_i = \frac{1}{\sigma_i^2}$$

In this case, and provided that the distributions of the measurement error are normal, the estimate obtained is the *maximum likelihood* estimate. Under the same premise it is also possible to obtain standard errors of the model parameters as the square root of the diagonal elements in the covariance matrix.

Weighting of PET Data

The variance of reconstructed PET data is dependent on many factors, including the duration of the acquisition, the time since the scan start which needs to be compensated by a decay correction, scatter and random correction, the sampling volume, the reconstruction method, etc. Therefore, PET variance models used in weighting of the residuals during fitting are always approximations.

In his presentation *Parameter Estimation: Least squares and why it gives you fits* (Handouts of Pharmakokinetic Course 2009) Richard E. Carson gives the following hints on using weights:

- Uniform weights (ordinary least squares fitting): Even if the data does not have uniform variance the estimates should be unbiased, but the parameter standard errors will be higher than they could be.
- Wrong weights: The greater the error in the weights, the larger the loss of precision in the parameter estimates (more important for ^{11}C than ^{18}F).

2.2   Reference Tissue Models

The measurement and analysis of the blood samples for kinetic modeling is an invasive and demanding procedure. Therefore, methods have been developed to obviate the need for invasive blood sampling. The solutions found replace the arterial input curve by an indirect input curve, namely the time activity curve of some reference tissue. Therefore they are called *reference methods*. Reference methods are not able to provide a full kinetic analysis. However, assuming certain relations between the kinetics of the tissue of interest and the reference tissue, they can provide valuable measures of interest.

Most of these reference methods are dedicated to reversibly binding neuroreceptor tracers. A reference tissue must be found which is devoid of receptors, and then it is assumed that the distribution volume of the non-displaceable compartment (free tracer in tissue and non-specific binding) is the same among the tissues. Under these assumptions a measure of the receptor concentration called *binding potential* can be calculated from the two time-activity curves.

Model Structure

The compartment models are usually based upon the following configuration:
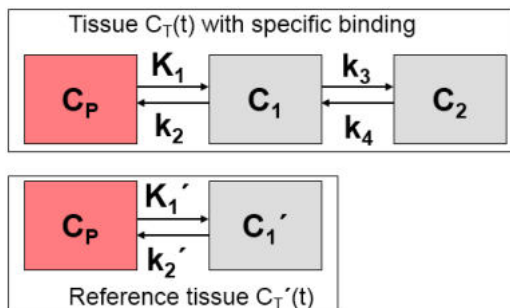
In the model equations C'(t) represents the TAC from the reference region (k_3=0 in the 2-tissue compartment model), and C(t) the TAC from a receptor-rich region (k_3>0).

However, the various reference methods differ in their mathematical approaches, and they show substantial differences with regard to noise sensitivity and processing speed. They are described in the PKIN Model Reference $\boxed{151}$ section.

2.3   Spectral Analysis (SA)

The closed-form solutions of compartment models involve the convolution of the input function with decaying exponentials. Based on this observation, a generalized technique called spectral analysis (SA) was introduced by Cunningham and Jones [66]. The operational equation of SA is given by

$$C_{Tissue}(t) = \sum_{i=1}^{N} a_i C_P(t) \otimes e^{-\beta_i t} = \sum_{i=1}^{N} a_i B_i(t)$$

$$C_{Model}(t) = (1 - vB)\, C_{Tissue}(t) + vB\, C_{Blood}(t) \cong C_{PET}(t)$$

that is, tissue uptake is modeled as a sum of N possible tissue responses. Due to the constraint of first order tracer kinetics, the coefficients a_i and the decay constants bi must be non-negative. In practice, a discrete set of the decay constants β_i is selected which covers the physiologically reasonable range, typically logarithmically spaced in the range [10^{-5},1]sec^{-1}. The corresponding tissue responses

$$B_i(t) = C_P(t) \otimes e^{-\beta_i t}$$

are the basis functions of spectral analysis.

When fitting the operational equation above to a tissue TAC, the only unknowns are the coefficients a_i, because only a pre-defined set of discrete β_i values is considered. Therefore, the problem is that of a non-negative linear least squares estimation (NNLS) with the constraint of non-negative coefficients. There is a well-known NNLS algorithm available [67], which allows readily calculating the optimal set of a_i coefficients. They allow calculating the model function and visualizing it together with the tissue TAC in the same way as for the compartment models.

An advantage of SA is the fact that no particular compartment structure is imposed. Rather, its result can be used to estimate how many kinetic tissue compartments can be resolved by PET. To this end, the results are plotted as a spectrum with the selected decay constants β_i along the x-axis (as the "frequencies") and the estimated coefficients a_i along the y-axis (as the "amplitudes"). Because of the large range, log(β_i) is used in spectrum plotting rather than β_i. The number of peaks in this spectrum corresponds to the number of distinct compartments. A peak appearing to the far left (low frequency, slow component) indicates irreversible trapping. A peak to the far right (high frequency, fast component) corresponds to kinetics indistinguishable from the input curve, thus to vascular contributions. Intermediate peaks represent compartments which exchange reversibly with plasma or with other tissue compartments [68].

The examples below used synthetic data generated using compartment models without noise and blood contributions. In the first example the simulated tissue TAC of a 1-tissue compartment model was fitted by SA with 500 basis functions. It is evident that, because of the discrete nature of the β_i basis, the compartment was split into two neighboring frequencies. The adjacent amplitudes are usually summed to provide the combined peak height for a compartment.
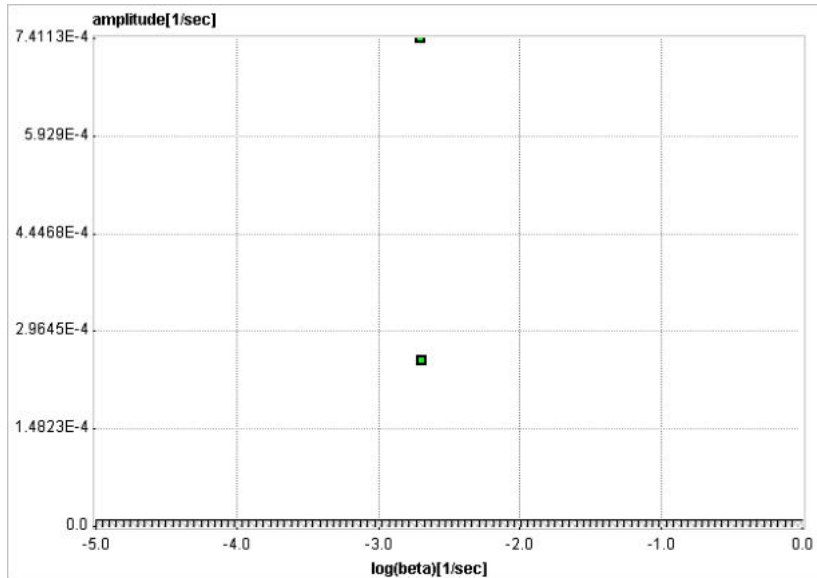
In the next example an irreversibly trapping compartment was added (k3>0, k4=0) to the same first compartment. The corresponding peak is clearly seen to the left of the spectrum.
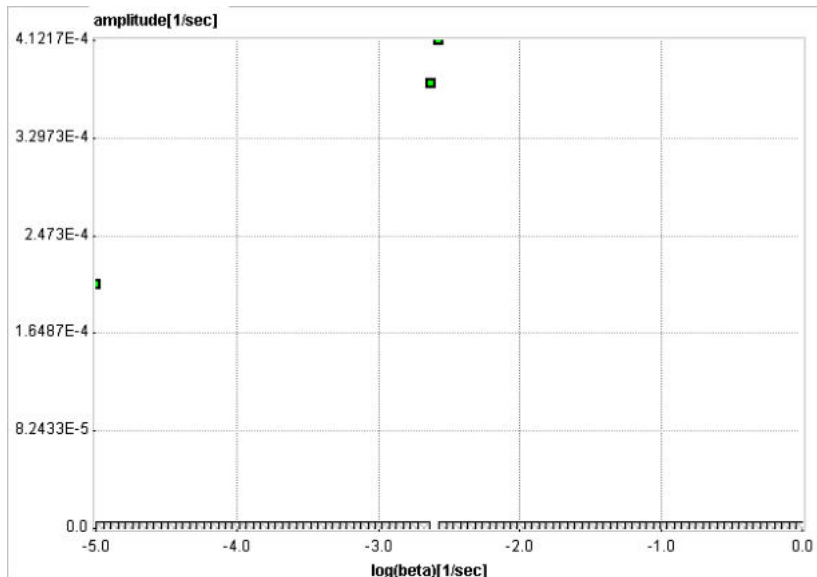
When changing kinetics to become reversible (k4>0), the second compartment appears as a second peak in the inner of the spectrum.
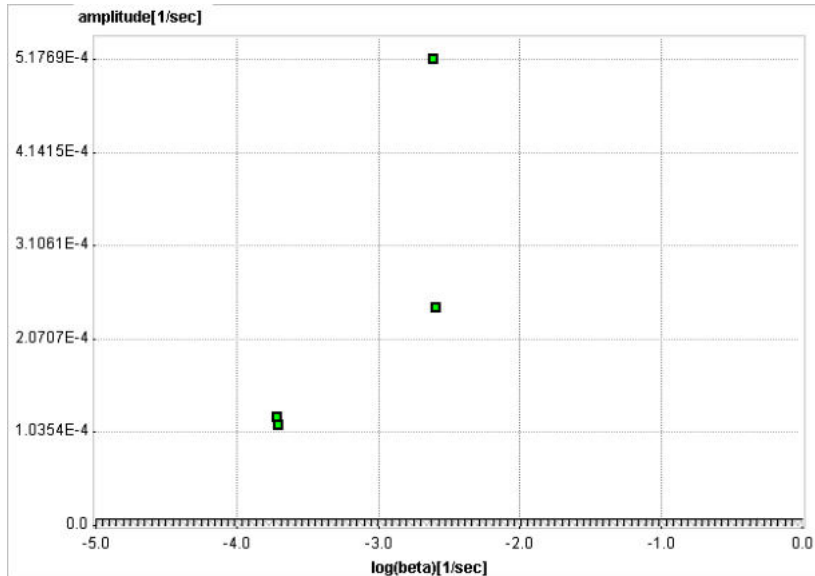
In general it is not possible to calculate the compartment rate constants from the spectral analysis outcome. However, an estimate of K_1 can be obtained as the sum of the peak amplitudes

$$K_1 = \sum_{i=1}^{N} a_i$$

and an estimate of the distribution volume V_T as

$$V_T = \sum_{i=1}^{N} \frac{a_i}{\beta_i}$$

An additional information which can be calculated is the impulse response function

$$IRF(t) = \sum_{i=1}^{N} a_i e^{-\beta_i t}$$

The impulse response function completely describes the system, and the expected tissue TAC for any given input function and can simply be calculated by convolution with the IRF:

$$C_{PET}(t) = C_P(t) \otimes IRF(t)$$

In the practical application of spectral analysis potential problems were found: Caution should be applied when interpreting the number of peaks [66], and the error properties of the estimates are difficult to assess [69]. Several authors have proposed variants to overcome these problems [70,71], but in current practice spectral analysis is not yet frequently applied.

3   *PKIN Configuration*

There are two places where the functionality of PKIN tool is configured: the available models and their order in the list in the global PMOD configuration, and the other settings in the tool-specific configuration.

3.1   **Global Configuration**

Use the

 Config

button on the PMOD ToolBox to open the general configuration dialog window. The PKIN models are available on the **PKIN models** sub-panel of the **USERS** configuration.
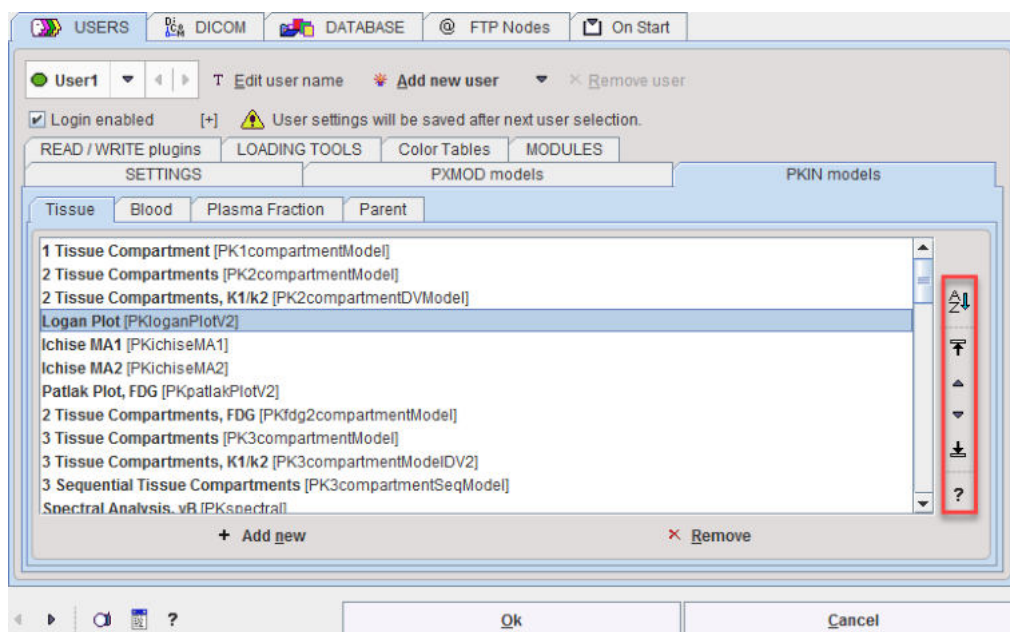
Note that there are four different types of models, for **Tissue**, **Blood**, **Plasma Fraction** and **Parent**, each with a dedicated panel. The example above shows the **Tissue** panel which consists of the list of configured models, and tools to change the list. All of these panels behave in the same way.

A list entry shows in bold the model name as it appears in the PKIN interface, and in parentheses the actual file name of the model plug-in. The order how the models appear in list and consequently in the PKIN application can be changed by please selectin an entry and moving it up/down using the arrows to the right or alphabetical sorting. The **?** button will bring up a window with a short model explanation. To remove unneeded models for shortening the selection just select entries in the list and activate **Remove**. Correspondingly, the **Add** button shows a dialog window with model currently not configured, so that they can be added again.

3.2 Local PKIN Configuration

The configuration of PKIN can be adjusted by **Kinetic**/**Settings**/**Modify**
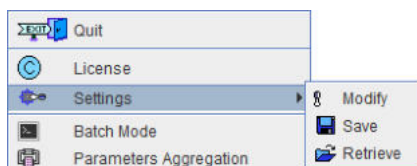
or using the configuration button ![config] from the status line. It opens the following dialog with the current definitions, which can be modified. The **Paths** tab allows setting the initial data paths of file-based loading as well as the file extension filters.
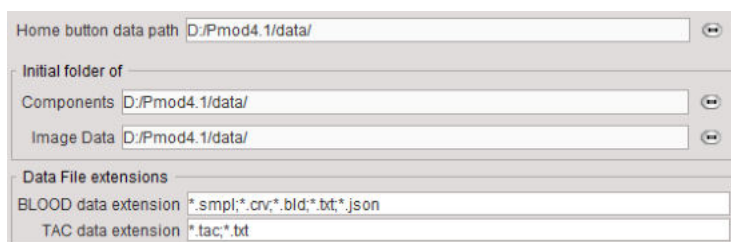
The **Display** pane gives access to the settings of the initial PKIN appearance and the appearance of the report page.
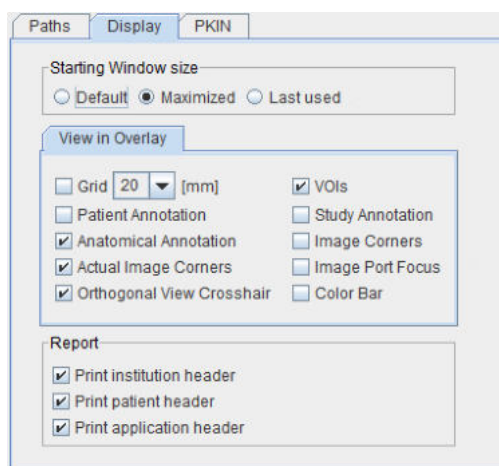
The **PKIN** pane shows the current models of tissue, whole blood, plasma and the parent fraction with their respective default parameters. Changing the parameters here and saving will establish new default parameters.

The next section allows specifying the time and value units of data loaded from text files. If the header lines in the data file do not contain valid units, these units are applied to the imported data.

The lower section serves for modifying the layout:

- **Curve controls position** allows displaying the curve controls to the **Right**, **Left** or at the **Bottom**. Their purpose is to optimize the layout depending on the display aspect ratio. **Left** and **Right** are recommended for wide screen systems, otherwise **Bottom**.

- **Center model parameters display**: If this box is enabled the parameters area is centered vertically within the available space.

- **HD curve model display**: If this box is checked the model curves are calculated for display purposes at many intermediate points, not just at the measurement times. The result is a smooth appearance of the model curves. However, when exporting the model curves, these interpolated points may be disturbing. Note that for the fitting only the original acquisition times are used.

4   *PKIN Data Processing*

4.1   General Assumptions in PKIN

The following is generally assumed:

- All loaded data has been **decay corrected** to the same time point. This means that the PET scanner and the blood sampling times must have been synchronized. An exception is the processing of dosimetry data, which is preferably not decay corrected.

- The acquisition time intervals may have gaps, but must not overlap.

- The **whole blood** curve $C_{Blood}(t)$ represents the activity concentration of the tracer and all its metabolites in whole blood samples.

- Most PET models require the **input curve** $C_P(t)$, namely the authentic tracer in arterial plasma which can exchange with tissue. Depending on how the plasma-related information is prepared and loaded, the input curve needs to be calculated differently 41.

- In compartment models the whole-blood signal contribution can optionally be considered in the operational equation by
$C_{Model} = vB*C_{Blood} +(1-vB)*C_{Tissue}$
where v_B represents the fractional volume of the blood space in the VOI, $C_{Blood}(t)$ the whole blood concentration, and $C_{Tissue}(t)$ the summed concentrations in all tissue compartments.

- The results of non-cardiac flow models are returned per cm^3 tissue. To convert to flow per g tissue the values must be divided by the tissue density.

Exceptions to these rules are specified in the description of the individual models.

4.2   Processing Overview

Data processing of studies with PET or SPECT tracers typically consists of the following parts:

1. Data Loading	- Create a new workspace (tab) in the PKIN tool. - Load the whole-blood curve (total activity concentration of tracer in the blood samples). - Load the plasma *activity* curve. Depending on the preparation of the blood data the plasma activity curve can represent the unchanged tracer (parent) in plasma, or total tracer in the plasma of the blood samples including the metabolites. In the latter case of total tracer the metabolite correction has to be performed in PKIN. - An alternative to loading the plasma activity curve is loading the plasma *fraction* curve. In this case the total plasma activity is calculated by multiplying whole blood activity with the plasma fraction. - Load the parent fraction curve (fraction of unchanged tracer in plasma). This is only necessary if the loaded plasma curve represents total tracer activity in plasma including metabolites. - Load the average time-activity curves of one or multiple tissue regions.
2. Input Curve Configuration	- Define interpolation functions (also called models) for the different types of blood data and fit them to the data. The default is linear interpolation between measurements, and a parent fraction identical to 1. - The input curve is obtained as the multiplication of the plasma model with the parent fraction model.
3. Kinetic Model Configuration	Select a region with a "typical" time-activity curve (TAC) from the **Region** list.

	- Select a simple model from the **Model** list. - Enable the parameters to be fitted by checking their boxes; unchecked parameters remain at the initial values entered. - Select a weighting scheme of the residuals; variable or constant (default) weighting is available.
4. Kinetic Model Fitting	- Fit the model parameters by activating the **Fit current region** button. - Consult the residuals to check whether the model is adequate; there should ideally be no bias in the residuals, just random noise. - If the model fit is fine, configure **Copy the model to all regions** to **Model & Par** and activate the button to establish the same initial model configuration for all TACs. Then activate **Fit all regions** to adjust the parameters to the regional measurements. - Check the fit result for all the TACs by stepping through the regions. - If the model is not yet fine, test more complex models.
5. Kinetic Model Comparison	- Switch between compartment models of different complexity and fit. The parameters are either maintained for each model type, or converted, according to the **Model conversion** setting in the **Extras** panel. - The results of the different fits are stored in the **Model History** which can be used for easy switching and for the results comparison per region. - Check the residuals for judging model adequacy. - Check the different criteria on the **Details** tab (Schwartz Criterion **SC**, Akaike Information Criterion **AIC**, Model Selection Criterion **MSC**) to decide whether a more complex model is supported by the data. - Check for parameter identifiability. As an indicator of the parameter identifiability standard errors (**%SE**) are returned from the fit. They should remain limited for all relevant parameters. Additionally, Monte Carlo [84] simulations can be performed to obtain distribution statistics of the parameter estimates. - If justified by physiology, try to improve the stability of parameter estimation by enforcing common parameters among regions in a coupled fitting [64] procedure. - Compare the outcome of compartment models with that of other models, such as reference models or graphical plots.
6. Saving	- Save all model information together with the data in a composite text **.km** file which allows restoring a session including the fitting history. - Save a summary of all regional parameters in an EXCEL-ready text file **.kinPar**.
7. Batch Processing	Lengthy calculations such as coupled fits with many regional TACs or Monte Carlo simulations can be run in a batch job [87]. The results are saved both as .km files and in an EXCEL-ready text file.

4.3   Starting the Kinetic Modeling Tool

The kinetic modeling tool is started with the **Kinetic** button from the PMOD ToolBox
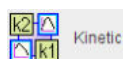
or by directly dragging kinetic modeling (.km) files onto the above button.

4.3.1 User Interface

The user interface is organized as illustrated below. The left part of the display visualizes the data, the model and the fit. The green squares represent the tissue measurement values (tissue time-activity curve, TAC), the red circles the input curve, the yellow circles the blood spillover curve (whole blood time-activity curve), and the blue line the calculated model curve with the current model configuration shown to the right. All curves can be shown or hidden using the check boxes in the control area.

The lower curve display shows the weighted residuals, i.e. the difference between the measurement and the model curve multiplied by a weighting factor. Unweighted residuals can also be shown.

The right part gives access to the different models and operations which are described in the following sections.

The **taskbar** to the right provides shortcuts to loading and saving, as well as the configuration of frequently used model filters and fitting options.
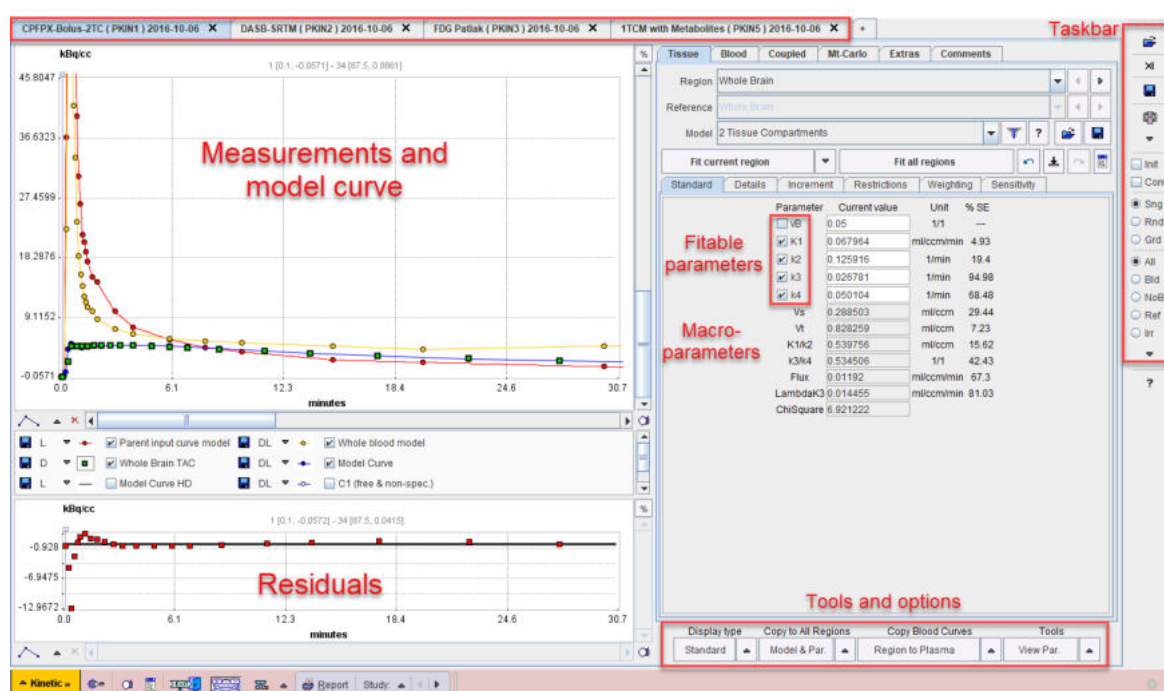
4.3.2 PKIN Menu

The **Kinetic** menu is located in the lower left corner and is mainly used for data operations such as loading, saving or closing. Additionally
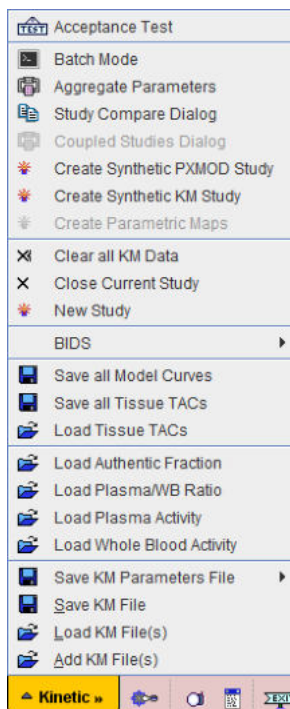
Loaded data sets can be added into new workspaces, so multiple data sets can be available simultaneously and selected for processing using named tabs.

Acceptance Test	Self test of the program testing 26 model configurations. It is executed automatically the first time PKIN is started.
Batch Mode	Open interface for batch processing 87 .
Aggregate Parameters	Aggregate 98 the results from different KM Parameter Files in a single table for statistical analysis.
Study Compare Dialog	Open a PKIN dialog window with the same data so that two model configurations can be examined side by side in separate windows.
Coupled Studies Dialog	Fit multiple data sets 68 together, keeping selected parameters synchronized.
Create Synthetic PXMOD Study	Generate a synthetic image series 106 which has a different combination of model parameters in each pixel.
Create Synthetic KM Study	Generate a synthetic modeling data set 105 from the current data with ideal tissue TACs and potentially modified timing.
Create Parametric Maps	If the TACs have been transferred from PVIEW to PKIN and the images are still open in PVIEW, open a dialog window 110 for assembling the resulting parameters into images. If average TACs were transferred, the VOIs will be homogeneous showing the regional result. If pixel-wise TACs were transferred, the VOIs will be filled by parametric maps.
Clear all KM Data	Close all workspaces.

Close Current Study	Close currently selected workspace.
New Study	Open a new, empty workspace.
BIDS	WIP implementation for creating data sets according to the emerging Bioimaging Data Structure.
Save all Model Curves	Save the model curves of all regions in a tab-delimited text file.
Save all Tissue TACs	Save the tissue TACs of all regions in a tab-delimited text file.
Load Tissue TACs	Load ⌐35⌐ the tissue TACs from a tab-delimited text file.
Load Authentic Fraction	Load a fraction ⌐46⌐ curve representing the ratio of parent (aka authentic, intact, unchanged) tracer to total tracer in plasma.
Load Plasma/WB Ratio	Load a fraction curve representing the ratio of total tracer in plasma ⌐44⌐ to whole-blood.
Load Plasma Activity	Load a curve representing total tracer in plasma ⌐44⌐.
Load Whole Blood Activity	Load a curve representing tracer in whole-blood ⌐43⌐ samples.
Save KM Parameters File	Save the parameters ⌐41⌐ of all regional tissue models in a tab-delimited text file (.kinPar).
Save KM File	Save all data ⌐41⌐ of the current workspace with all model configurations in a proprietary KM text file (.km).
Load KM File(s)	Load a number of selected KM files into separate workspaces, clearing already loaded data.
Add KM File(s)	Load a number of selected KM files into additional workspaces, keeping existing data.

4.3.3 Curve Layout

The curve display supports the visualization of the different loaded measurement as well as the calculated model curves. The available curves depends on the selected tab.

Curves with selected Tissue Tab

After data loading the time-activity informations of the current region are shown in the curve display in a default layout. The large area contains

- the green **TAC** values representing the tissue TAC of the selected **region**, in the example the **Whole Brain TAC**;
- the red **Parent input curve model** which is used as the input curve for the model calculations;
- the yellow **Whole blood model** used for blood spillover corrections;

▪ and the blue **Model Curve** which results from evaluating the current model configuration with the input curve.

Per default, only the **TAC** and the **Model Curve** are enabled for display by the check box in the control area. Depending on the context, there are additional curves available for display but hidden (box not checked). In the example below the compartment concentrations C_1 and C_2 of the 2-Tissue compartment model as well as a finely resolved **Model Curve HD** could also be shown by checking their boxes.
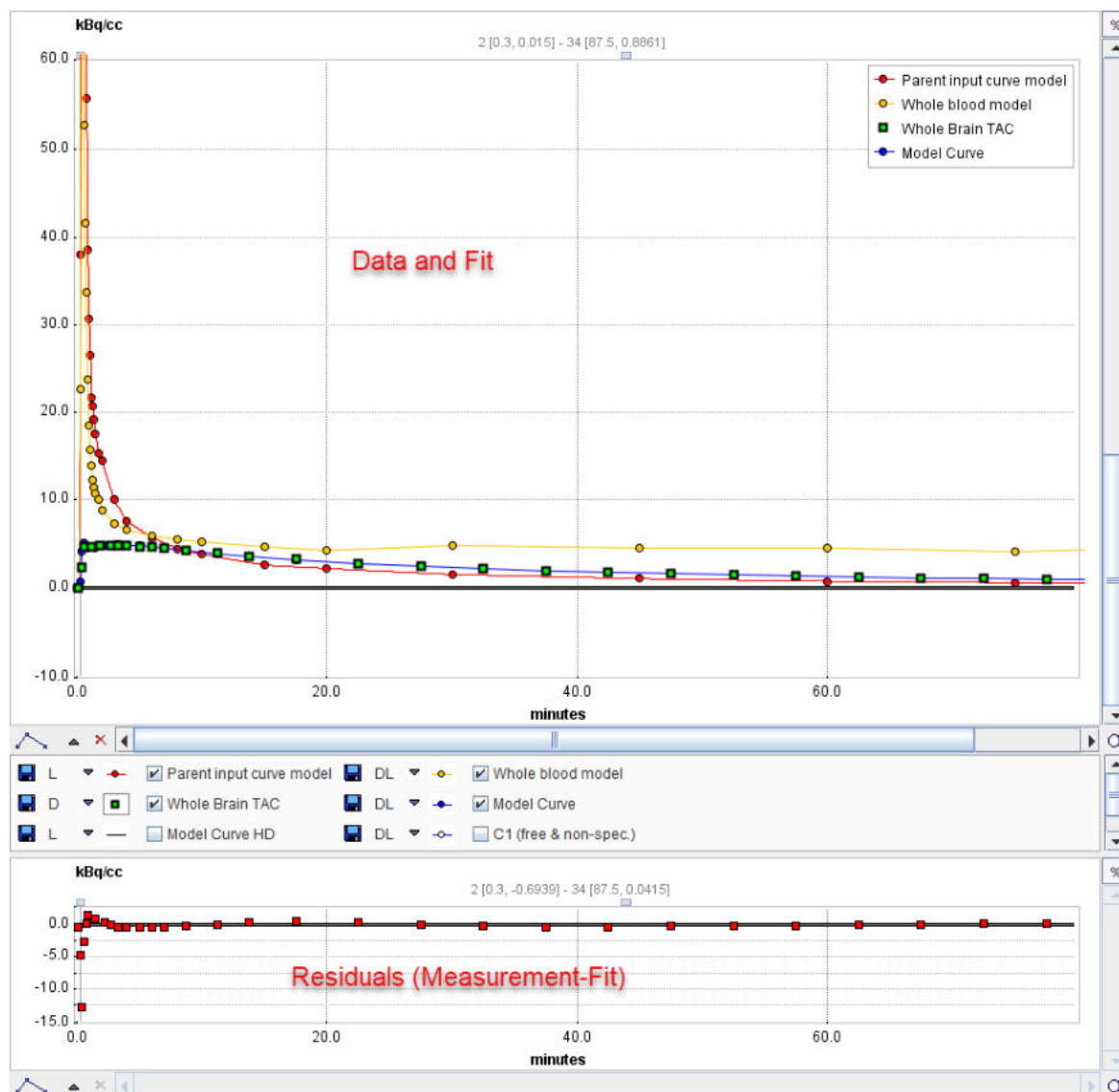
The smaller curve display at the bottom visualizes the difference between the measured TAC and the model curve. Note that for screens with limited hight it may be convenient switching the configuration 21 to the layout with the curve controls to the right instead of below.

The general manipulations available in the PMOD curve display are explained in the next section.

4.3.4 General Curve Display Functionality

A common curve display object is used in all PMOD tools. It consists of a curve area and a controls area underneath.
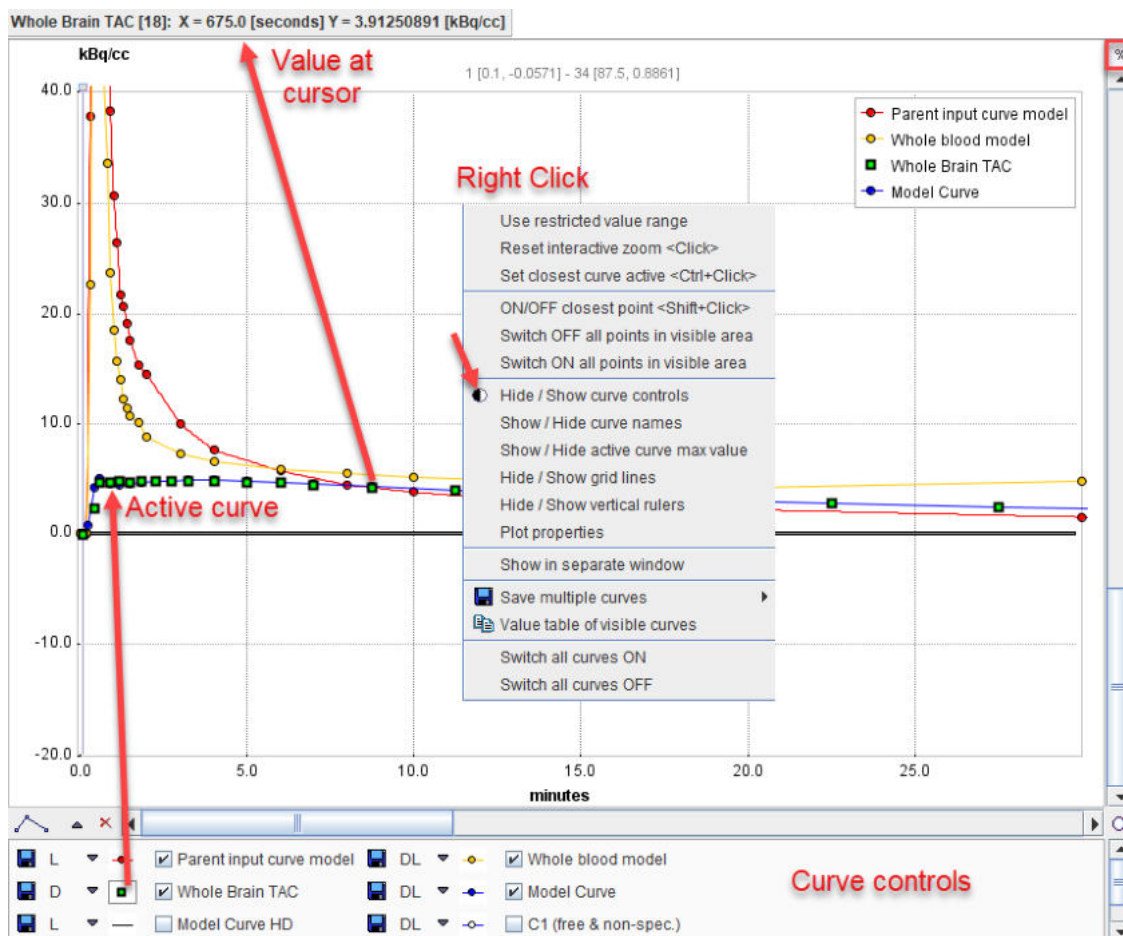
In some situations the control area may initially be hidden. In this case, please open the context menu by right clicking into the plot area, and select **Hide/Show curve controls**.

Curve Area

The curve area shows the curves which are enabled for display. There is always an *active curve*, which is shown in bold. A curve can be made active by holding down the CTRL key and clicking at one of its points, or by pushing its button in the controls area as illustrated with the **Model Curve** above.

The definition of the active curve is relevant for the tools which interrogate the curve values:

- There are two small handles at the top of the curve area: a little rectangle to the left, and a line to the right. These are handles which can be moved left/right using the mouse, and the gray vertical lines move with them. The values at the top center of the curve area represent the interpolated (x/y) values of the active curve at the location of the handles. To get the measurements of a different curve just CTRL+Click at that curve to get the values updated.

- Only in some curve displays: When the cursor is brought close to a point of the active curve, its x/y value pair is shown at the upper left of the curve area.

To *zoom* into an area of the curve just click the left mouse button to the corner of the area of interest and drag a rectangle. After releasing the mouse button the display is zoomed into the defined rectangle. An alternative is to define the axes **Range** in the context menu. A single mouse click into the curve area is sufficient to reset the zoom.

Context Menu

By clicking the right mouse button into the curve area a context menu with some additional options can be opened.
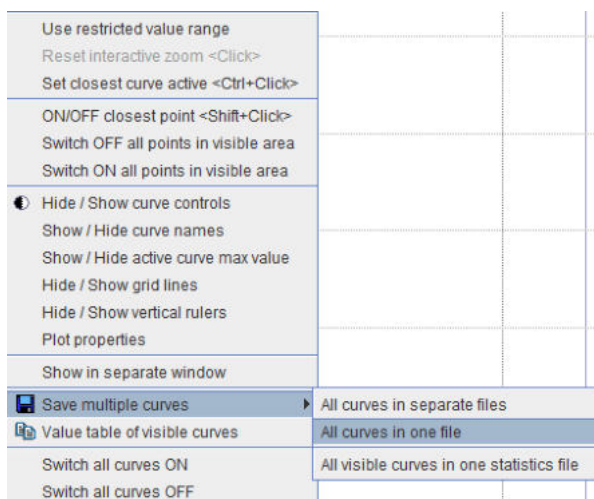
The functions are:

Use restricted value range

Set the range of the x- and y-axis by entering a numeric value.
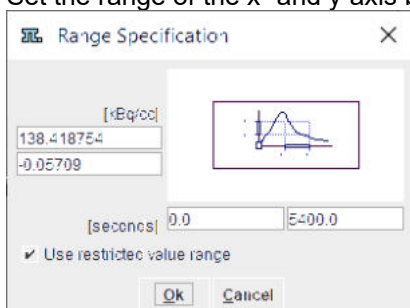
If the **Use restricted value range** box is checked, the range is maintained until the configuration is opened again and the check removed. Otherwise, a single click resets the range to the default.

Reset interactive zoom

To reset the curve range to the default full range. It is grayed if the display is not zoomed or the range is fixed.

Mouse operation: single `Click` into curve area.

Set closest curve active

Selects the curve nearest to the point clicked with the right mouse button when opening the context menu.

Alternative mouse operation: `CTRL+Click` at a curve.

ON/OFF closest point

Disable a measurement of the active curve. This is reflected by setting the symbol to gray.
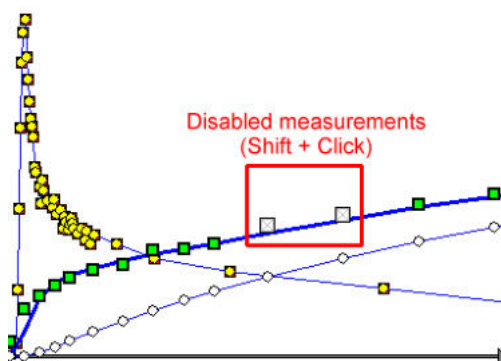
In the context of model fitting measurements marked in gray are regarded as outliers and not considered when evaluating the cost function.

Alternative mouse operation: select the relevant curve to active, then `SHIFT+Click` at measurement.

Switch ON/OFF all points in visible area
In combination with zooming this option allows to quickly disable/enable a section of the active curve.

◐ Hide/Show curve controls
Allows hiding the controls if the curve display area is small, and to show them again.

Show/Hide curve names
Controls, whether a box with the visible curve names is shown in the upper right. Note that if the available vertical space does not allow listing all names, the box is not shown.

Show/Hide active curve max value
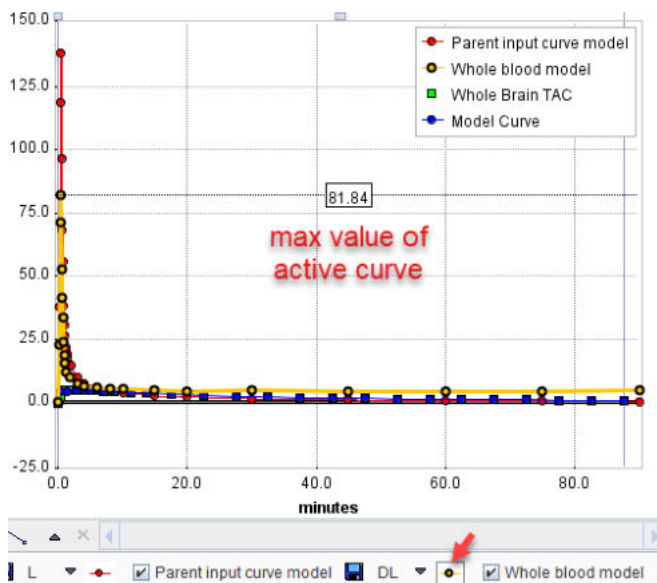
Hide/Show grid lines
Controls the display of the grid lines in the plot.

Hide/Show vertical rulers
Controls whether the rulers are shown which allow measurements on the active curve.
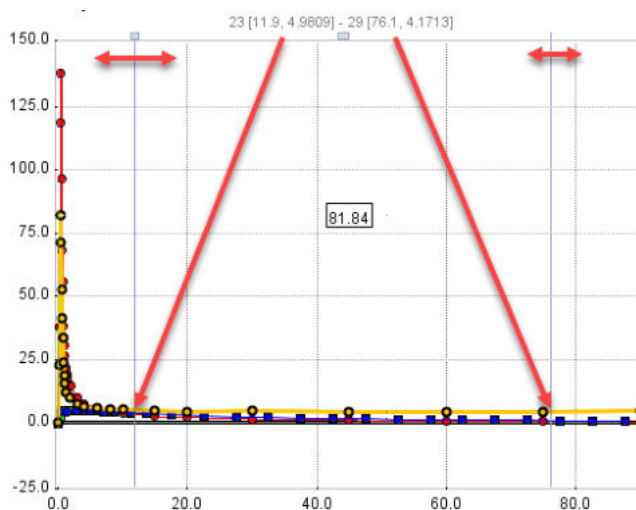
Plot properties
With this entry a configuration dialog is opened for setting the annotation **Font size**, for enabling **Curve antialiasing** (smooth curve appearance), and for excluding the horizontal and vertical zero lines.
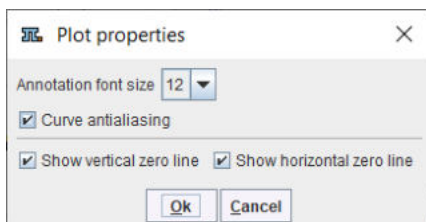
Show in separate window	With this option, the curve display can be opened in a separate, large window to closely examine the plot.
Save multiple curves	Allows saving the numeric data of the curves in a single or separate text files.
Value table of visible curves	Opens a dialog window which shows the numeric values of all visible curves in a dialog window. The window contents can be copied to the **Clipboard** and pasted to a different application.
Switch all curves ON/OFF	To quickly change the visibility of all curves. When switching all off, the active curve is still shown.

Curve Control Area

The control area lists the curves which are available for display. There are several elements to modify the curve appearance:
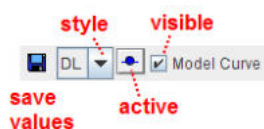
Show/Hide	To show/hide a curve check/uncheck the *visible* box.
Active curve	To set a curve to active click at the *active* button, or directly `CTRL+Click` on the curve itself. The line/symbols get bold.
Style	The list selection can be used to change the style of a curve:
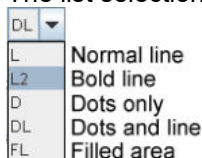
Further useful interface elements:
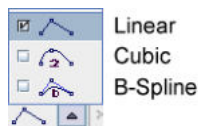
Changes the shape of the lines defined by the measurements.

Note that calculations are not based on the display representation of a curve.

Saves the numeric data of the curve as a text file with two columns. These files obtain a **.crv** suffix and can easily be opened in Excel or a text editor.

When working with a database the curve can be attached to a particular image using the **Attach to Patient (Serie)** in the appearing dialog.
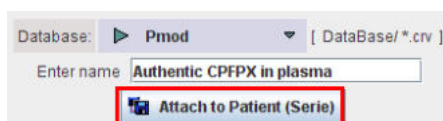
If this button is enabled, each curve is normalized to its own maximum and shown as percent values. This mode is helpful for

comparing shapes when the dynamic range of the curves is very different.

Creates a capture of the curve area. The captured image can be saved as a **JPEG**, **TIFF** or **DICOM** file. It can also be copied to the **Clipboard** to paste it into some office application.

4.4 Data Loading/Saving

4.4.1 File-based Data Import

There are slightly different formats for the time-activity data of blood and tissue. With blood data it is assumed that instantaneous sampling was performed at well-defined time points. With tissue data it is assumed that the measurements represent the average tracer concentration during a certain observation period, the PET frame duration defined by start-time and end-time.

4.4.1.1 Data Units

Timing Units

The following timing units are supported.

- **[milliseconds]**
- **[seconds]**
- **[minutes]**
- **[hours]**

During data loading, a conversion of the timing information to seconds is performed.

Value Units

The unit **[1/1]** is generic. In this case the user has to take care that all data used for modeling have been translated into compatible values.

PET data typically arises in concentration units, which are a requirement for modeling. The following activity concentration units are supported.

- **[Bq/ml]**, **[Bq/cc]**, **[kBq/cc]**, **[MBq/cc]**
- **[uCi/cc]**, **[nCi/cc]**
- **[kcps/cc]**

Note: During PET data loading, the unit specification will be used to **convert the specified activity concentration values into the internal representation of kBq/cc**. All activity concentration data will be displayed in kBq/cc in the user interface.

The formats for CT and MRI data are **[HU]** and **[1/1]**, respectively.

The unit string in square brackets should immediately follow the column headers as described in the following sections. If units are not defined or not recognized, it is assumed that the units specified in the PKIN **configuration** 21 apply.

4.4.1.2 Import of Blood Data

PET tracers are usually applied by intra-venous injection and then brought to the tissue of interest by circulation. Often, a part of the tracer may be bound to red blood cells. Another part may be processed in organs and end up as labeled metabolites circulating in blood plasma. The remaining

category of tracer in plasma is the unchanged (authentic) tracer (parent) which is available for exchange with tissue and represents the *input curve* relevant for modeling.

In PKIN, the following four types of blood data are supported to model the contributions of the different forms of tracer in blood to the expected PET signal:

1. The concentration of all forms of tracer in **Whole Blood** samples: As the average signal from a VOI always contains a fraction of signal from blood vessels and capillaries, the concentration in whole blood is needed for modeling the blood content in the expected PET signal.

2. The concentration of all forms of tracer in plasma (**Plasma Activity**) : Although the unchanged tracer in plasma is required as the input curve of the models, it is common practice to measure the tracer activity of the whole plasma sample.

3. The fraction of unchanged ligand in plasma (**Parent Fraction**): As a result of the metabolite analysis of plasma samples, the relative concentrations of the unchanged tracer and the metabolites are known. This information is represented by the ratio of unchanged tracer to total tracer. This fraction is expected to start with a value of 1 at the time of injection (all tracer is unchanged), and gradually decreases as the metabolites build up. Since plasma analysis is often experimentally complex and therefore error-prone, it is advisable to fit a smooth curve to the measured parent fraction.

4. The **Plasma Fraction**: An alternative to using the measured plasma activity is the use of the ratio of plasma activity to whole blood activity, called the "Plasma Fraction". If the plasma fraction is known it can be multiplied with the whole blood activity to obtain the plasma activity. For tracers without metabolites this obviates the need for the actual blood analysis.

Whole Blood and Plasma Activity

The whole blood and plasma activity concentrations must be prepared in text files, and can be loaded using **Load Whole Blood Activity** and **Load Plasma Activity** from the **Kinetic** menu. Such text files with the blood data can be prepared for example in MS Excel and then saved as tab-delimited or csv separated text files. There are two variants of the format:

1. Separate files for whole blood and plasma activity. In this case separate files are prepared with a header line, the sample time in the first column and the sample value in the second column as illustrated below:

sample-time[seconds]	plasma[kBq/cc]
0	0
6	0.01
12	0.02999997
18	37.94988615
24	118.4692892
30	138.4187542
36	96.68874303
42	68.22877186
48	55.90871407
54	38.498845

sample-time[seconds]	whole-blood[kBq/cc]
0	0
6	0
12	0.02
18	22.64
24	71.19
30	81.84
36	52.8
42	41.62
48	33.72
54	23.76

2. A composite file containing both whole blood and plasma activity. Note that in this case the keywords **sample-time**, **plasma** and **whole-blood** are required to define the meaning of the

columns.

sample-time[seconds]	plasma[kBq/cc]	whole-blood[kBq/cc]
0	0	0
6	0.01	0
12	0.02999997	0.02
18	37.94988615	22.64
24	118.4692892	71.19
30	138.4187542	81.84
36	96.68874303	52.8
42	68.22877186	41.62
48	55.90871407	33.72
54	38.498845	23.76

Plasma and Parent Fractions

The plasma and parent fractions need to be prepared in a similar file

time[minutes]	parent-fraction[1/1]
0	0.27184857
0.5	0.986298884
1	0.980287666
1.5	0.96249071
2	0.92520486
2.5	0.865100226
3	0.779710538
3.5	0.666156902
4	0.645169911
4.5	0.558181271
5	0.577178078
5.5	0.50647541
6	0.480742985

and loaded using **Load Plasma/WB Fraction** or **Load Fraction/Parent** from the **Kinetic** menu.

Notes
1. If no whole blood data is loaded into PKIN, the plasma concentration is used for blood spillover correction.
2. If the activity of unchanged tracer in plasma is loaded instead of the total plasma activity, no correction with the parent fraction is required. No further action is required in this case, because per default it is assumed that the parent fraction equals the constant of 1.
3. There are models which require two input curves, and in principle models with up to 10 input curves can be handled in PKIN. For these models the loading sub-menues contains appropriately labeled entries.

4.4.1.3   Import of Tissue Time-Activity Data

Tissue time-activity curves are similarly organized in tab-delimited text files. The frame start and end times are arranged in the first two columns. Next come columns with the measurements from different tissues. Note that the TAC value units are specified after the heading of the *second* column.

start[seconds]	end[kBq/cc]	amy re	amy li	mtl re
0	60	2.29234465	1.98046206	2.74814255
60	120	5.01681393	6.57439037	6.81311774
120	180	6.18648905	5.47218649	6.87476477
180	240	6.57449309	6.58147725	7.33382369
240	300	5.95458466	6.59546425	7.65397945
300	360	7.06336248	7.3919664	7.21261065
360	420	7.07207865	8.066492	6.83445489
420	480	6.44191169	7.89309654	7.34035093
480	540	5.73063921	5.38436545	7.231256
540	600	6.35527845	7.03980869	7.31066749
600	900	6.04079722	6.51268169	6.96765792

Tissue time-activity curves are loaded using **Load Time Activity Curve** from the **Kinetic** menu.

> **Note:** This data import assumes that all curves have the same timing. If it is differing, the timing has to be edited after loading using the Edit Data [102] facility, or the data need to arranged in the Composite Format [36] which supports individual timing.

4.4.1.4   Composite Import Format for all Data (.kmData)

The composite format allows including all types of blood and tissue data into a single tab-delimited text file. The advantage is that all data can be prepared externally and loaded at once, and that such files can directly be used for batch processing.

File Start

The file starts with the two lines

```
# APPLICATION
KINETIC_MODELLING_DATA
```

It is followed by a sequence of sections for the data and other related information.

Demographic and Study Data

The demographic information and study-related data can be defined in a section headed by the **# PATIENT** tag. Each line starts with a tag in capital letters which is followed by a tab, and then the corresponding value.

# PATIENT	
// Id	Value
PATIENT_NAME	PKIN1
PATIENT_ID	Dyn. CPFPX bolus & MRI
PATIENT_BIRTH_DATE	01.01.1981
PATIENT_SEX	M
PATIENT_SIZE	1.79
PATIENT_WEIGHT	75
PATIENT_REFERRING_PHYSICIAN	Dr. B
PATIENT_INSTITUTION	
PATIENT_ACQUISITION_DATE	20060302130226
PATIENT_SERIES_DATE	20060303130226
PATIENT_STUDY_DATE	20060301130226
PATIENT_STUDY_ID	CPFPX Bolus
PATIENT_ACCESSION_NO	
PATIENT_STUDY_DESC	CPFPX Bolus
PATIENT_SERIES_DESC	Dynamic PET
PATIENT_BODY_PART	BRAIN
PATIENT_LATERALITY	
PATIENT_RADIOPHARMACEUTICAL	
PATIENT_RADIO_NUCLID	C-111A1/SRT/^18^Fluorine/
PATIENT_HL_TIME	6586.2
PATIENT_UNIT	kBq/cc
PATIENT_ACTIVITY_PRE	280
PATIENT_ACTIVITY_POST	0

Comments

Comments can be included for describing the data and recording important facts. The **# DESCRIPTION** section allows specifying text which will be imported with the data and can be shown in the user interface. [104] The three elements to enter in a line are the **Date** of the comment, the **User** who edited it, and the actual comment text as the **Description**.

# DESCRIPTION		
// Date	User	Description
09.04.2015 09:46	John	First comment text
09.04.2015 11:17	Anna	Second comment text

Further comments can be added as lines preceded by a **//** in a **# NON_PMOD_COMMENTS** section. They are only for documentation purposes of the raw data and not interpreted by PKIN.

```
# NON_PMOD_COMMENTS
// This is a comment
// Without any interpretation in PMOD
```

Model Specification

A tissue model can optionally be specified in a **# MODELS** section.

# MODELS		
// ID	Model	Name
KINETIC	PKepideprideModel	3_Comp._Metabolites

The **Model** entry corresponds to the class name, and the **Name** entry to the string shown in the model list. Both can be determined in the configuration utility as illustrated below.
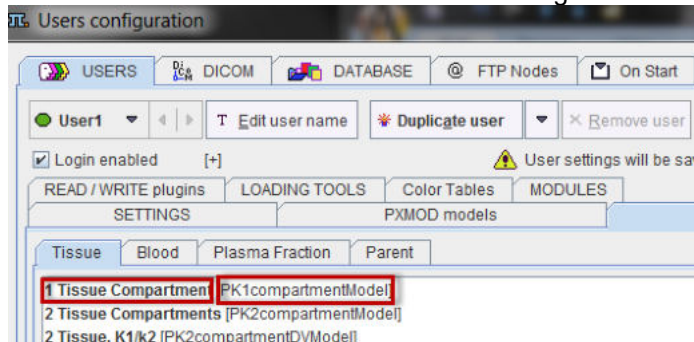
For reference models the reference region can be specified in by an additional line with the **REFERENCE_REGION** tag.

# MODELS		
// ID	Model	Name
KINETIC	PKichiseMRTM	Ichise Reference MRTM
REFERENCE_REGION	1	KH re

Note that the region number (starting from 0) is relevant, not the region name.

Data Sections

Each data part to be included is specified in a section starting with a line **# DATA** followed by a header line of the actual data. For blood data the following format is supported. Note the data units which are specified in the brackets directly after the column names in the header line.

# DATA **Section start**	
// sample-time[minutes]	whole-blood[kBq/cc]
0.75	1.67E-05
1.5	4.818734894
2.25	18.47443512
3.02	21.04629028
3.75	27.0131493
4.52	12.99452924
5.25	8.306559731
6.1	5.448897549
7.98	3.980082036
10.07	3.663062688

For tissue data, it is assumed that the first two columns define the acquisition start and end times, whereas the following columns contain the data for the different tissue regions.

# DATA					
// start[seconds]	end	tac.first-region[kBq/cc]	volume.first-region	tac.second-region[MBq/cc]	volume.second-region
0	60	0.457384501	2.2	0.49	2.29
60	120	1.339319209	2.2	1.39	2.29
120	180	1.674894667	2.2	1.69	2.29
180	240	1.960293448	2.2	1.99	2.29
240	300	2.120504157	2.2	2.19	2.29
300	420	2.372558724	2.2	2.39	2.29

Each region is represented by a column with header **tac.**name, where "name" will be shown as the region name in PKIN. Two regions will result from the example above, with names **first-region** and **second-region**. Again, the data units are specified in brackets, directly after the region names. Optionally, the volumes corresponding to the TAC can be defined in additional columns, indicated by the header **volume.**name. The volume unit is cc, so there is no need to specify it.

Multiple blood and tissue data sections can be included in a composite data file, for instance to handle TACs with different timing. The following key words are parsed in the header lines.

sample-time	Timing of blood samples.
whole-blood	Activity of whole blood samples, to be used for spillover correction. May also be used for calculating the plasma activity if a plasma fraction is loaded.
plasma.1 **plasma.2**	Plasma activity of the first input curve, the second, etc. Plasma activity may represent the activity of parent, if the metabolite correction has been done outside of PKIN, otherwise the activity of parent and metabolites. In the latter case a parent fraction has to be loaded for the metabolite correction within PKIN.
plasma-fraction.1 **plasma-fraction.2**	Plasma fraction of the first input curve, the second, etc. These fractions will be multiplied with **whole-blood** for the calculation of **plasma.1, plasma.2** etc. Supported units: **[1/1]**, **[%]**.
parent-fraction.1 **parent-fraction.2**	Parent fraction of the first input curve, the second, etc. These fractions will be multiplied with **plasma.1**, **plasma.2** etc. for the calculation of the input curves. Supported units: **[1/1]**, **[%]**.
start	Start time of the PET/SPECT acquisition frames. The time units of the tissue TACs are specified after **begin**, eg. **end[seconds]**.
end	End time of the PET/SPECT acquisition frames. Note: if the values of the tissue TACs have common units they can be specified after **end**, eg. **end[kBq/cc].** `# DATA` <table><tr><td>// start[seconds]</td><td>end[kBq/cc]</td><td>tac.first-region</td><td>tac.second-region</td></tr><tr><td>0</td><td>60</td><td>0.457384501</td><td>0.676302078</td></tr><tr><td>60</td><td>120</td><td>1.339319209</td><td>1.157289596</td></tr><tr><td>120</td><td>180</td><td>1.674894667</td><td>1.294177216</td></tr></table>
tac.name	Tissue TAC column with the name specified after the **tac.** tag.
volume.name	Volume of the tissue TAC column with the name specified after the **volume.** tag. Unit of the volume is cc.
tac.reference **tac.cerebellum**	Tissue TACs with this label will be used as reference when applying reference tissue models, if **REFERENCE_REGION** is not specified in the model section.

File Format and Loading

The information described above can be saved in a tab-delimited text file (**.kmData**) or an **XLS** (Excel 2003, not xlsx) file and loaded with the **Load KM** file entry from the **Kinetic** menu. Alternatively, the file can be dragged and dropped onto the PKIN window or the PMOD ToolBox.

4.4.2 Data Import from VOIs

An important usage of the VOI analysis is the generation of time-activity curves (TAC) for subsequent kinetic modeling. This can easily be achieved in PVIEW by the following steps

VOI Definition

The image data is loaded as a dynamic series with the *correct acquisition times* and the *correct input units*. This is important, because otherwise the acquisition start/end times in kinetic modeling will be wrong, and the TACs may be different in magnitude with respect to the blood data. Such problems result in erroneous model parameters.

In dynamic image series there is generally not enough anatomical information to delineate VOIs. Often, averaging of a subset of the acquisition frames resolves the problem. The VOIs are then delineated in the summed images, transferred to the dynamic images, and optionally saved to a file.

TAC generation

Switch the tool to the dynamic study, and activate the button

A dialog window appears which is organized in three panels:

1. The left area allows defining the proper type (TISSUE, WHOLE BLOOD) of the calculated TACs and selecting the regions to be sent to the **Kinetic modeling** tool.

2. The central area shows the TACs.

3. The right area controls the displayed TACs. Additionally, the **+-** buttons allow for simple arithmetic operations with the curve values before transfer to PKIN.
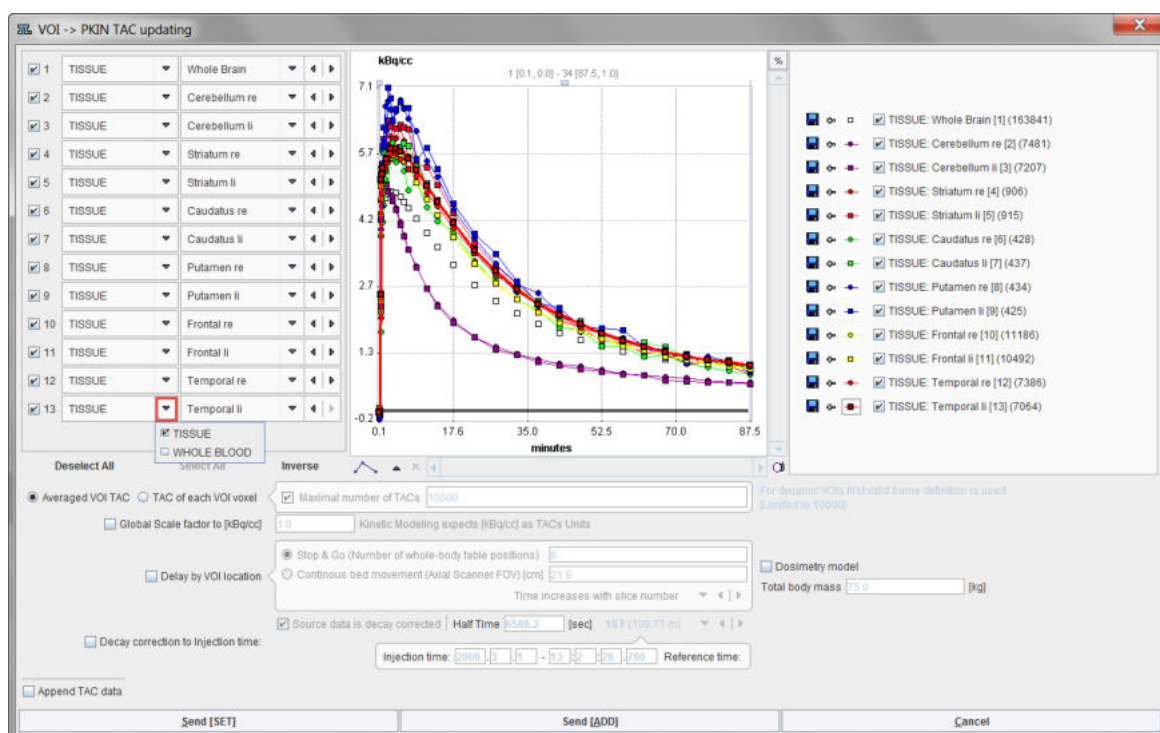
Average TACs

The standard and default procedure is to use the signal average in the VOIs, corresponding to the radio button **Averaged VOI TAC**. With this setting, not only the average is calculated and transferred, but also the standard deviation which may be used for weighted fits in PKIN.

Voxel-wise TACs

When the transfer mode is set to **TAC of each VOI voxel**, the individual voxel-wise TACs are transferred. There is a maximum number of TACs which will be considered for the transfer, per default set to **10'000**. The number of voxels in the selected VOIs is shown in brackets in the control section. Naturally, the standard deviation is zero in this case.

TAC Value Operations

The calculated TAC values can be modified in two ways.

1. Every individual curve has a **+-** button which allows multiplying the values with a factor, dividing, adding or taking the logarithm.
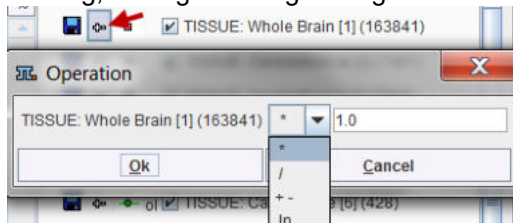
2. All generated curves can be scaled with a factor defined by the **Global scale factor to kBq/cc** option.

TAC Time Shifting

If image data acquisition requires multiple table positions (e.g. dynamic whole-body PET), the timing between VOIs may differ. The timing relative to the injection is crucial for modeling and also for dosimetry. Therefore, the **Delay by VOI location** option is supported
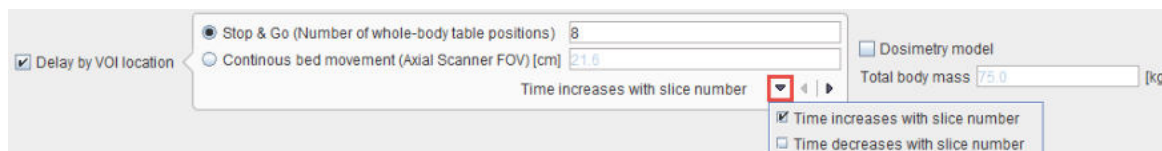
with two alternatives:

- **Stop & Go** corresponds to the standard acquisition mode with the table halting in adjacent, overlapping field of views. As there is usually not enough information in the image headers to know for each slice the exact timing, the timing of the different table positions is obtained by dividing the acquisition duration by their number.

- **Continuous bed movement** assumes that the patient is scanned while the table is continuously moving. Here the axial scanner field of view is required for approximating the time when a VOI is scanned.

Note that the timing derived from these settings can only be approximate and may need correction. The resulting timing of the TAC curves is updated in the curve window whenever one of the settings is changed. Depending on the scanning, the time shifts may be applied in the wrong direction. For instance, the bladder curve may start before the brain curve although the data was acquired in head-in position. To rectify such a case there is a switch **Time increases with slice number**/**Time decreases with slice number**.

Dosimetry Model

If the flag **Dosimetry model** is enabled, the **OLINDA Residence Times** model will be set after the TAC data have been transferred to the PKIN tool together with the **Total body mass** of the patient. This information is extracted from the demographic information in the image, and can be edited if it is not present.

Decay Correction

If the **Decay correction to Injection time** flag allows correcting the TACs to a n injection time which may be before the first acquisition. If the **Source data is decay corrected**, only a scaling factor is applied. Otherwise, a time-dependent correction is used.
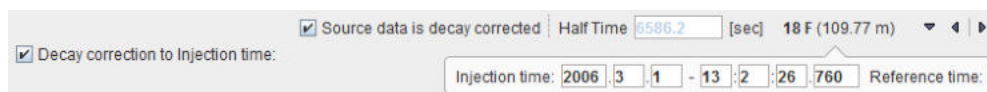
Data Transfer

The **Send** buttons initiate the transfer of the activity curve data to the PKIN tool. Selecting **Send[SET]** transfers the TACs to the currently selected tab in an open PKIN tool. With the **Append TAC Data** box checked, the curves are appended as new regions to the existing data, otherwise the current data is over-written. **Send[ADD]** first creates a new tab in PKIN, to which the data is added. If PKIN is not running, the tool is first started and the data added.

Both the average value and the standard deviation within the VOIs are transferred, as well as patient and study related information. The standard deviation may be used for weighted fits in PKIN.

4.4.3   Data Saving

Data can be saved in various formats using the following **Kinetic** menu entries:

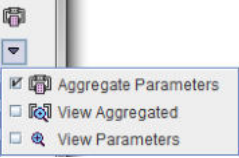|	
Save KM File	Saves all data and the configuration in a comprehensive text file with suffix **.km**. Loading a .km file restores the state of the previous processing with the exception of the display settings.
	Note that the model fitting history |59| is also saved/retrieved.
Save KM Parameters File	Generates and saves a summary of the model parameters with their standard error in all regions.
	Note: The results of the latest **Fit** in the model fitting history |59| are exported, rather than the currently viewed parameter set which may be manually changed.
	Result is a tab-delimited text file with extension **.kinPar**, which is readable with any text editor and with numerical programs such as Excel. There is a **Save** and an **Append** sub-menu, the latter for combining results of several studies in a single file. **kinPar** files can be aggregated |98| for performing statistical analyses. Saved model parameters can be inspected using the **View Parameters** button from the taskbar to the right.
Save all Time Activity Curves	Saves just the regional time-activity data in a multi-column text file with **.tac** extension. This option may be helpful to export TAC data for visualization in a different program.
	Another useful application of **Save/Load Time Activity Curve** is to append a TAC from a different tissue: first save the current TACs, add the TAC of an additional region as a new column in Excel, then load the **.tac** file again.
Save all Model Curves	Exports the tissue model curves of all regions into a text file. Note that these curves are not interpolated between the frame mid-times. To obtain smoother curves please use the **Create Synthetic KM Study** menu item.

Note: Units of the saved data TAC are always [kBq/cc] and [seconds].

4.5   Preparation of Blood Data

Types of Blood Information

PKIN supports four types of blood data which together allow computing the **input curve** [13].

1. The tracer activity concentration in whole blood. This information is used for the spillover term in the compartment models as well as in combination with the plasma fraction.

2. The total activity concentration of tracer in the plasma part of the blood.

3. The plasma fraction (concentration ratio of tracer in plasma to tracer in whole blood). The plasma fraction is multiplied with the whole blood concentration to calculate the total concentration of tracer in plasma.

4. The parent fraction (concentration ratio of unchanged tracer to total tracer in plasma). The parent fraction is multiplied with the total plasma concentration to calculate the input curve.

Note that the plasma options 2. and 3. above are excluding each other. If plasma activity has been loaded, the plasma fraction option cannot be used. On the other hand, if the plasma fraction has been loaded, the plasma activity option cannot be used.

Input Curve Calculation

The input curve is defined as the activity concentration of parent tracer in the arterial plasma. Depending on the imported data, the input curve needs to be calculated differently. Some typical scenarios are:

*   External metabolite correction: In this case the loaded plasma activity concentration already equals the input curve.

*   Use of parent fraction: In this case the plasma activity concentration (which should equal total activity in plasma) is multiplied with parent fraction for calculating the input curve.

*   Use of plasma fraction: In this case the whole blood activity is multiplied with the plasma fraction for calculating the plasma activity concentration. If the plasma fraction includes the metabolite correction part, the plasma concentration already represents the input curve. Otherwise, a parent fraction needs to be loaded, and the input curve results from multiplying the whole blood curve with the plasma fraction and then the parent fraction.

In practice, PKIN behaves as follows:

*   As soon as a whole blood activity concentration curve is loaded and no other information is available, it is also used as the input curve. To this end the plasma mode is set to "fraction", and a **Fix** plasma fraction model is applied with a factor of 1.

*   As soon as a plasma activity concentration curve is loaded, any plasma fraction data is discarded, and the plasma mode set to "activity". The activity interpolation mode defaults to **Lin. Interpolation**. The setting of the parent fraction is not changed.

*   As soon as a plasma fraction curve is loaded, any plasma activity concentration data is discarded, and the plasma mode set to "fraction". The fraction interpolation model defaults to **Lin. Interpolation**. The setting of the parent fraction is not changed.

*   A parent fraction equal to 1 is applied as long as no parent fraction curve is loaded, or no analytical parent fraction model selected. Correspondingly, the input curve corresponds to the plasma activity concentration.

Organization of the Blood-related User Interface

The different blood-related informations are readily available for configuration via the radio buttons **Whole blood**, **Plasma** and **Metabolites** on the **Blood** tab as illustrated below.
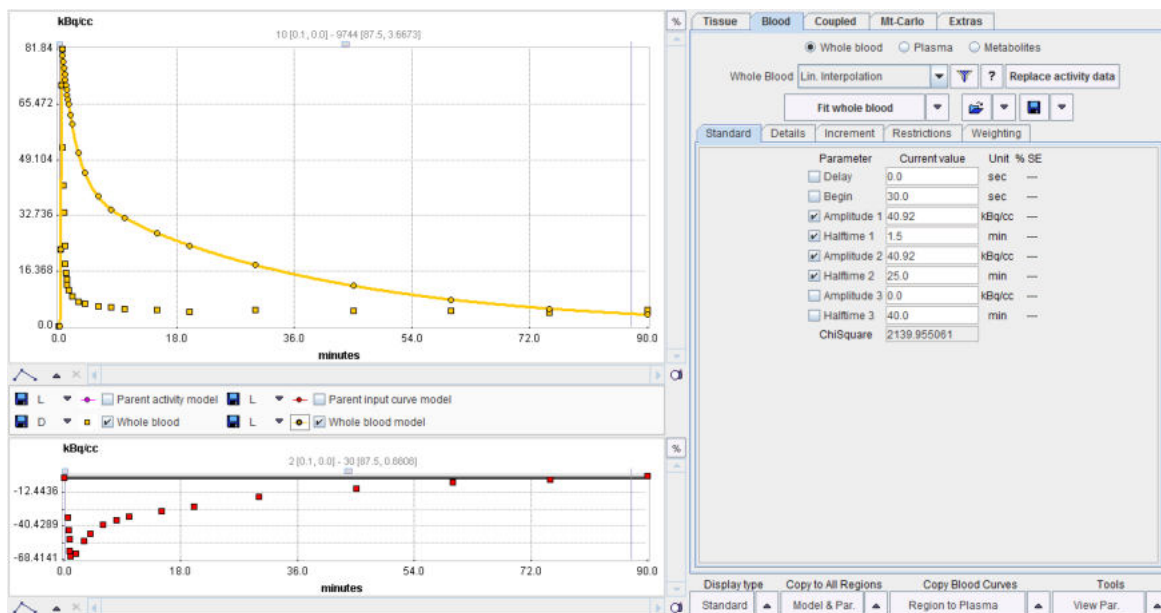
4.5.1 Interpolation of Blood Data

The tracer activity in blood is normally only sampled at a few time points during the acquisition. However, when calculating the operational equations (eg. by numerically integrating a system of differential equations), the blood activities must be available at any arbitrary time point during the acquisition period. This means that the blood curves must be interpolated according to some underlying model function. The interpolation models available for the different blood curves are described in the sections below.

4.5.2 Whole Blood

It is assumed that the time-course of the tracer activity in whole blood has been loaded with **Kinetic/Load Whole Blood.** To configure the interpolation model of whole blood please select the **Blood** tab, and set the **Whole blood** radio button. A list of models is available which can be shown with the arrow button indicated below.
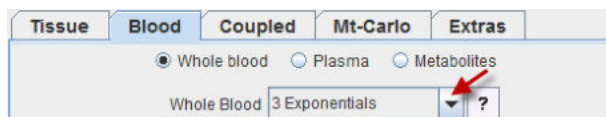
Default is **Lin. Interpolation**, which just represents linear interpolation between sample times. To replace linear interpolation by a smoother function select an appropriate definition from the list. As soon as a model is selected, the parameters are updated in the **Standard** pane, and a corresponding model curve is shown in the curve window as **Whole blood model**.
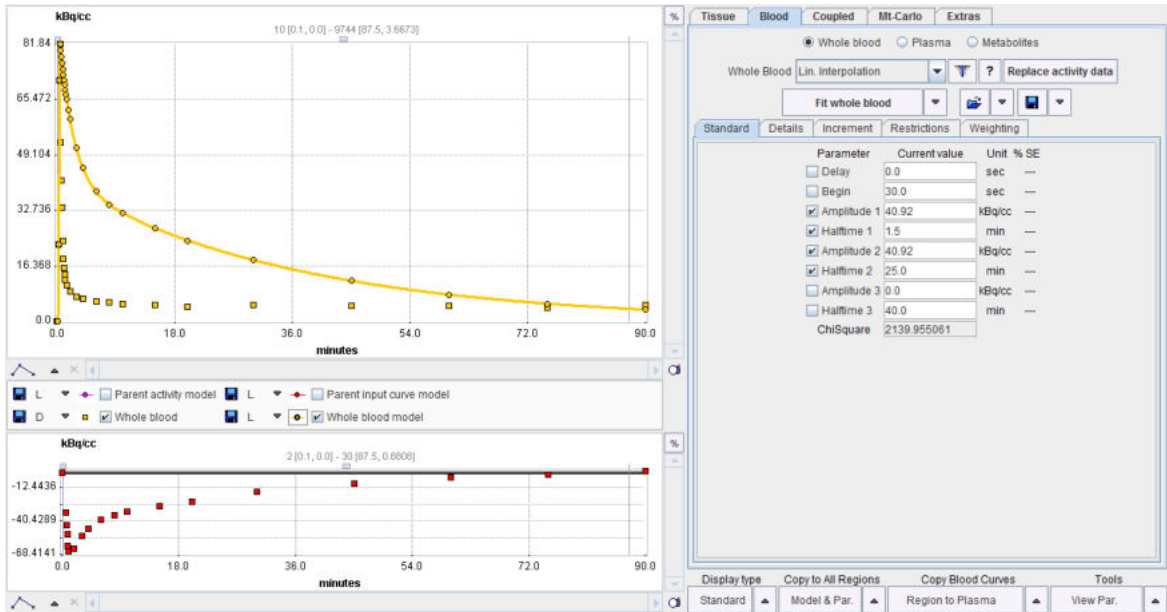
In the example above the model has not yet been fitted so that the distinction between the measurement and the model (sum of exponentials) is clearly visible. The parameters of the blood model can be configured for fitting purposes by enabling the check boxes. Activating the **Fit Whole Blood** button starts a fitting process which adjusts the model parameters such that the interpolation curve comes into optimal agreement with the measurements. Fitting works exactly in the same way as was explained for the tissue models below 53.

Replace activity data will replace the actual data samples by the current model values at the original sampling times. This functionality is mostly useful for replacing a blood curve by its dispersion-correction as described in a separate section 90.

The Blood Delay Parameter

All standard blood models have a **Delay** parameter to correct for a timing error between tissue and blood data. Positive delays represent delayed blood information and hence shift the blood curves to earlier times (to the left). This parameter is only relevant for fitting of the *tissue* model. Therefore, when fitting the *shape* of the blood curve with **Fit whole blood**, it is automatically *disabled*. When fitting the kinetic tissue model 71, however, it can be allowed for fitting.

4.5.3   Plasma

Plasma Activity

Here it is assumed that the time-course of the tracer activity in the arterial plasma has been loaded with **Kinetic/Load Plasma Activity**. The configuration and fitting of the interpolation model works in exactly the same way as for **whole blood** 43.

Please select the **Blood** tab, and set the **Plasma** radio button. Note the label **Plasma activity** label which indicates that the current working mode uses measured activities, not a derivation from whole blood activity. The same list of models is available as for the plasma activity as for whole blood. The available models are described in the reference section **section** 196.
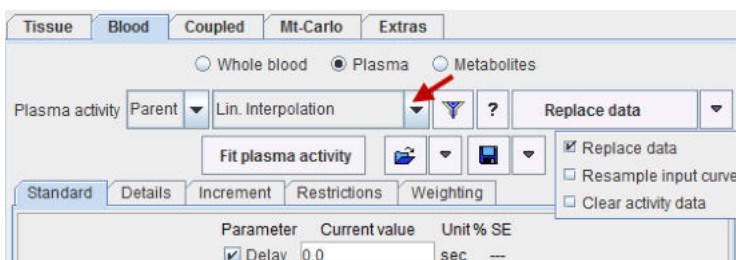
To the right of the model selection, there is an option button for changing the current data.

- **Replace data:** This function replaces the data samples by the values of the current model function at the original sampling times.

- **Resample input curve:** This function creates an explicit input curve from the current blood definitions. It resamples the input curve at the sampling times of the plasma curve and replaces the plasma measurements. Additionally, it sets the parent fraction to one, as any metabolite fraction is now included in the input curve. This approach may have advantages, if the plasma activity and/or the parent fraction can't be reasonably fitted, but their combination has a fitable shape.

- **Clear activity data**: This function discards the loaded plasma data and switches the mode to "plasma fraction". In that case the assumption is that an analytical plasma fraction function will be applied to the whole blood activity curve to derive the plasma activity.

Plasma/Whole blood Fraction

Here it is assumed that the time-course of the plasma fraction has been loaded with **Kinetic/Load Plasma Fraction**. To configure the interpolation model please select the **Blood** tab, and set the **Plasma** radio button.

Note the label **Plasma fraction** which indicates that the current working mode uses a function to derive plasma activity from whole blood activity. There is a list of models which can be fitted to the plasma fraction data. As soon as a model is selected, its parameters are shown in the **Standard** pane, and a corresponding model curve is displayed in the curve window as **Plasma fraction model**. The available models are described in the reference **section** 205, and **fitting** 47 works in the same way as explained for the tissue models.
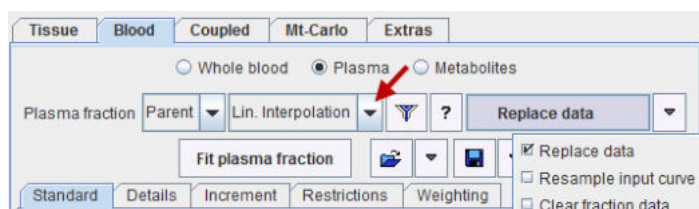

To the right of the model selection, there is an option button for changing the current data.
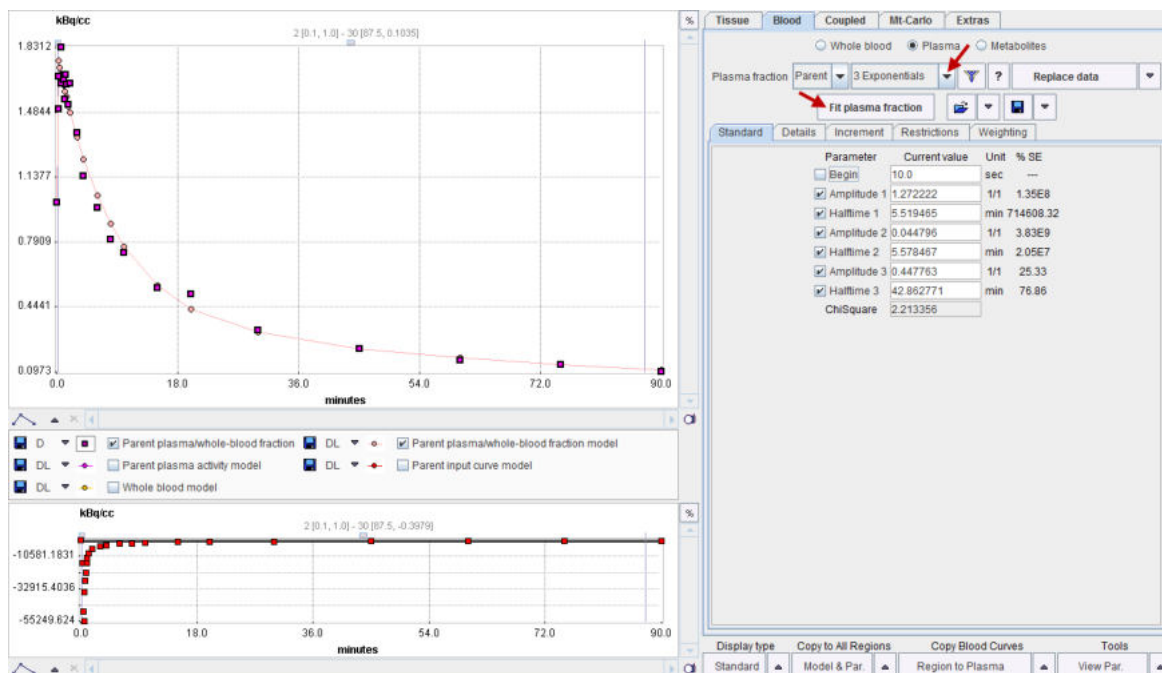
- **Replace data:** This function replaces the data samples by the values of the current model function at the original sampling times.

- **Resample input curve:** This function creates an explicit input curve from the current blood definitions. It resamples the input curve at the sampling times of the plasma curve and replaces the plasma measurements. It then switches back to "plasma activity mode" and sets the parent fraction to one, as any metabolite fraction is now included in the input curve. This approach may have advantages, if the plasma fraction and/or the parent fraction can't be reasonably fitted, but the input curve has a fitable shape.

- **Clear fraction data:** This function discards the loaded plasma fraction data. In that case the assumption is that an entirely analytical plasma fraction function will be applied to the whole blood activity curve in order to derive the plasma activity.

4.5.4 Parent/Plasma Fraction

- The transformation of the plasma activity curve into the input curve is governed by the configuration on the **Metabolites** tab. Two cases are to be distinguished.

Measured Parent Fraction Data is available

If a parent fraction curve has been loaded, it is shown in the curve area. Initially, the parent fraction model is set to **Lin. Interpolation** so that linear interpolation between the samples is used to calculated intermediate parent fractions. The model selection choice allows to select smoother models, and fit them to the measurements using the **Fit fraction** button as illustrated below.
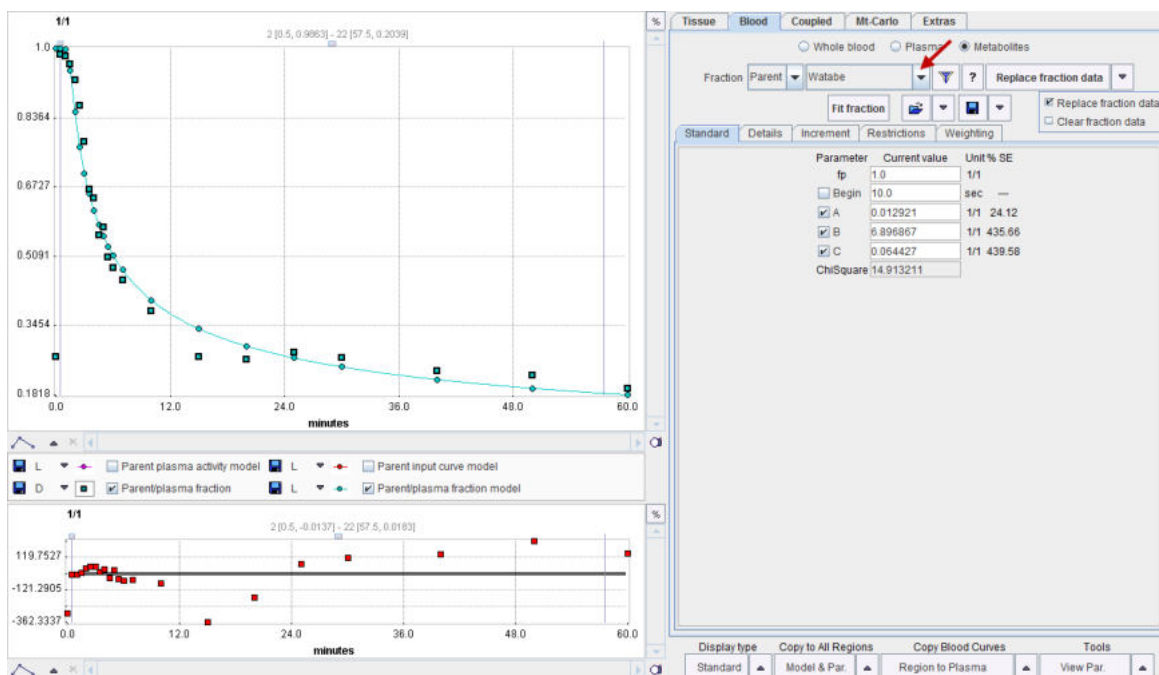
To the right of the model selection, there is an option button for changing the current data.

- **Replace fraction data:** This function replaces the data samples by the values of the current model function at the original sampling times.

- **Clear fraction data:** This function discards the loaded parent fraction data. In that case the assumption is that an entirely analytical parent fraction function will be applied to the plasma activity curve in order to derive the parent activity.

No Parent Fraction Data available

If no data parent fraction data have been loaded, the parent fraction model is set to **Fix** with a free parent fraction f_p=1. This is adequate for all tracers which do not require metabolite correction, and for cases when the metabolite correction has already been applied to the plasma data prior to loading them with **Load Plasma Curve**.

In the case of a tracer which shows a characteristic buildup of the metabolites it may be possible to derive an average parent fraction curve and fit a model to it. To apply a metabolite correction the user can then simply select the appropriate model function and enter the demographic parameter

values, as illustrated below. To apply a demographic correction, it must be ensured that time zero of plasma data always represents the time of tracer injection. Naturally, no fit will be possible in this situation.
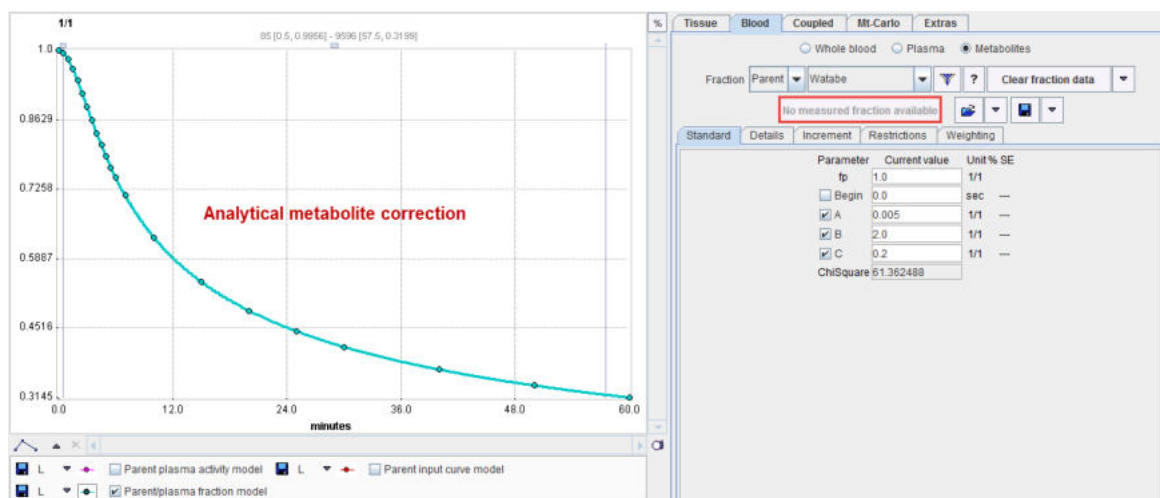
The available models are described in the reference section [211], and fitting [47] works in the same way as explained for the tissue models.

> **Note:** The metabolite correction is applied to the plasma curve using the original plasma sampling times. The assumption is that the parent fraction and the plasma curve have a common time scale. Only after the metabolite correction has been applied is the input curve shifted by the blood sampling time delay.

4.5.5 Default Model Configurations and Configuration Sets

All interpolation models allow the customization of the model default parameters, and the saving of specific configuration sets for certain task. The mechanism [51] is the same as described for the tissue models.

4.6 Configuration and Fitting of Kinetic Tissue Models

As soon as a kinetic model has been selected a model curve is calculated and shown in the curve display. The model curve represents the activity concentration values PET would measure if the model correctly described the observed physical processes. Fitting assumes that the model configuration is adequate and tries to find the set of model parameters for which the model curve is in optimal agreement with the measurement.

The following sections explain how a model is configured, fitted to data, and assessed for goodness-of-fit.

4.6.1 Kinetic Model Configuration

The main functionality for the definition and fitting of kinetic tissue models is available on the **Tissue** pane. The upper part contains data and model selections, while the lower part gives access to the model details and fitting results.
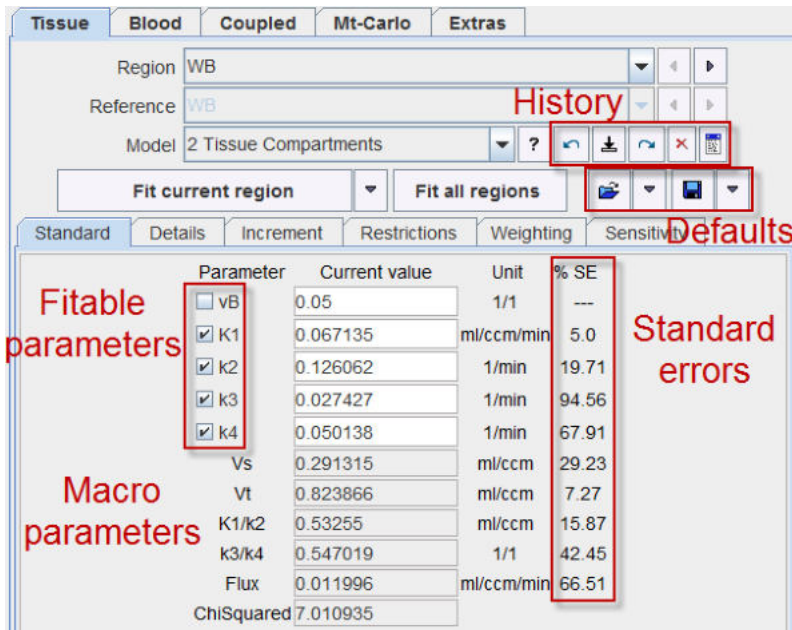
The main elements for the model configuration on the **Tissue** pane are:

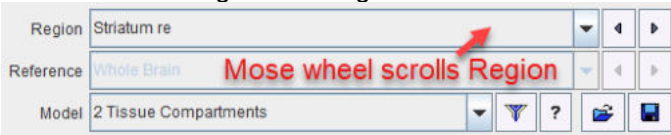|	
Region	When several regional TACs have been defined and imported, the current regional TAC can be set using this list selection. The left and right arrows allow stepping forwards and backwards through the TACs. It is possible to type the initial characters on the keyboard for quick selection of known regions, e.g. "st" to select the region named "striatum". After region switching, the display is updated with the configured model and the curves of the selected region. Note: when placing the cursor over the region selection, the mouse wheel can be used for fast region scrolling.
Reference	Selection of the regional TAC serving as reference in models which have the input curve replaced by a tissue TAC. Note that **Edit Data** allows creating a TAC averaged from several loaded TACs, which may be useful as a reference.
Model	The PKIN tool includes a comprehensive list of standard kinetic models and some auxiliary calculations. This list allows selecting among all currently configured models. As soon as the model is changed, the pane in the lower section is updated to show the parameters of this model. Note that the models in the list can be rearranged, added or deleted using the **PKIN Models** tab after selecting **Config** from the PMOD ToolBox. Furthermore, the list can be focused on the current analysis by filtering 52.
?	Button for showing a quick information about the current model.

4.6.1.1 Reference Models

When a reference **Model** is selected which uses the activity in a reference region as an implicit input curve, the blood-related items become disabled and the **Reference** region selection becomes active.
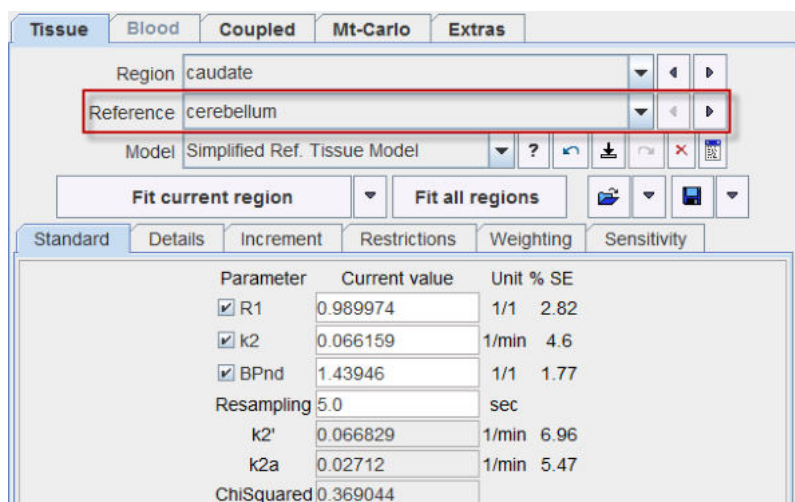
PKIN will pre-select a region containing "Cerebellum" or "Reference" in the name as the reference. If the selection is not adequate, please select the proper region from the **Reference** list.

4.6.1.2 Model Parameters

The **Standard** sub-tab illustrated above shows the configuration of the currently selected model. It encompasses different types of parameters:

- Input parameters which are needed to specify information used for model calculations.
- Fitable parameters which require a starting value and show the updated results after model fitting. A parameter is only optimized if its fit box is checked, otherwise it remains fixed.
- Macroparameters are calculated from model parameters in the upper part to instantly provide composite information such as the distribution volume or the flux.

The fitable and derived parameters have four columns of information:

- The **Parameter** name. In order to see a brief explanation of the parameter place the mouse pointer over the name. The explanation text is then displayed in the status line at the bottom.
- The **Current value**, which can be edited, and which is updated as the result of a fit.
- The **Unit** of the parameter value.
- The standard error **%SE** of the parameter expressed as a percentage of the parameter value itself. It is only available, if a fit has been performed using the **Marquardt-Levenberg** method.

4.6.1.3 Default Model Configurations and Configuration Sets

Model Default Configuration

Each model has default values. Initially, they are factory settings, but they can be re-defined by the user if he wants to establish a default configuration which is more adequate from him. There are four buttons next to **Fit all regions** for saving and retrieving the model configurations.
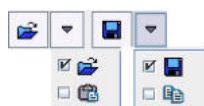
🔳	Save the current parameter configuration as the new default for the particular model type. Included are the values, the fit flags, and the restrictions of all parameters.
🔳	Resets the configuration of the current model to the saved defaults.

Note that the configuration defaults are managed on the basis of the PMOD login. Consequently, different logins could be prepared for processing types of data requiring different initial parameter values.

Complete Model Configuration Set

A model configuration can also be saved as an explicit definition file (**.kmModel**). It includes the tissue model as well as all blood models used. Included are the initial parameters, the fit flags, the restrictions and the residual weighting scheme (except for the prescribed weighting with the explicit weighting factors).

💾	Save the current model and parameter configuration in a file.
📂	Retrieve a model configuration.

The configuration files make it simple to establish defaults for particular data processing tasks: just load the appropriate .kmModel file and set it as the default. Another application is **batch processing** 87 . There, multiple models can be fitted to the data by simply selecting the corresponding .kmModel files.

4.6.1.4   Visualization of Parameter Effect

The **Increment** sub-tab is mainly used for visualization purposes. For each fitable parameter the current value is shown next to an increment value and an increment slider. When the arrow buttons are selected, the parameter value is incremented or decremented accordingly. The slider allows to increment/decrement a parameter smoothly. The minimal and maximal values for the slider as well as the initial increment are obtained from the values on the **Restrictions** tab.
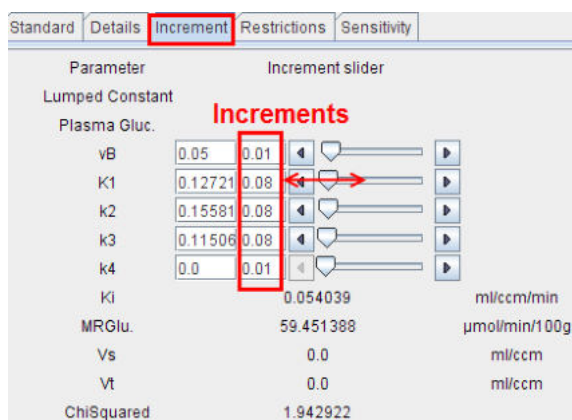
After every parameter change the curve display is updated, so that the user can observe its effect on the global uptake (model curve) and on the uptake in the different compartments ($C_1(t)$, $C_2(t)$).

For instance, as shown below, it can be nicely demonstrated that a change in K_1 simply scales the model curve, but does not change the curve shape: Set the curve display to relative scaling by selecting the **%** in the upper right and then change K_1. Nothing changes in the % display, provided that the blood volume fraction is set to 0. Any modification of the other parameters changes the curve shapes notably.
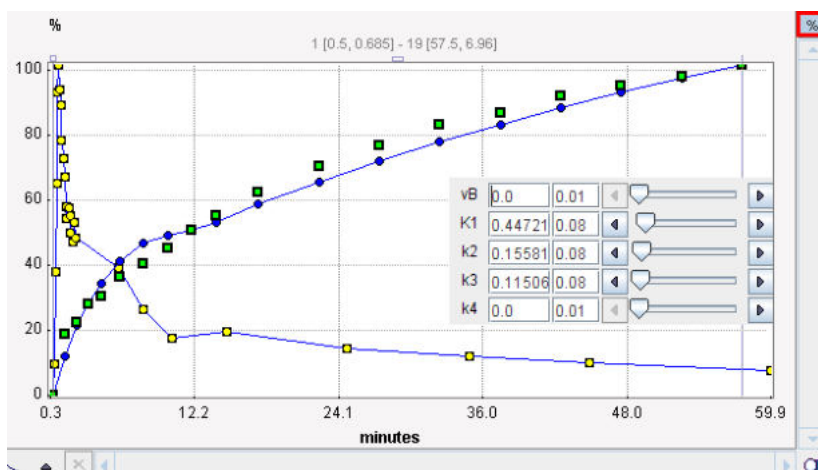
4.6.1.5 Parameter Restriction

The **Restrictions** sub-tab is relevant for fitting. For each fitable parameter there is a box for enabling the restriction which is defined by the **Lower bound** and the **Upper bound** value. The purpose of parameter restrictions is to ensure that the resulting parameters remain within a reasonable physiologic range. Without restrictions, there is a higher chance to end up with a meaningless solution. Note that these bounds are also used for the sliders on the **Increment** pane.

The **Search** value is used as an initial step-size for iterative fitting. It is recommended to set this value to about the same size as the parameter value itself, as it is automatically decreased if needed. This approach is not successful if the value is very small from the beginning.

4.6.1.6 Model Parameter Propagation/Conversion during Model Switching

The behavior of PKIN when switching between models is governed by the **Model conversion** check in the **Extras** pane, and the corresponding **Conv** option in the taskbar.

Model Conversion Disabled

The first time a model is selected for a particular region, the model default values are used. Thereafter, the most recent model parameter set as used for the same region is applied.

Model Conversion Enabled

Model conversion can be used to propagate parameter values from one model to another which includes the same parameter, or to convert compartment parameter values due to a change of model complexity [9].

- **Parameter propagation:** Parameter propagation allows to transfer the exact value of certain parameters from one model to another. This feature can for instance be used to fit a parameter using a robust method and propagate it to a more complex model where it is fixed during fitting. Examples of important propagated parameters are vB, t*, Flux, k_2'.

- **Parameter conversion:** When switching between models with the same number of compartments, the conversion is exact. If the number of compartments is decreased, the lumped parameters of the simplified model are calculated. If the number of compartments is increased, the same values are used for corresponding parameters, and the additional parameters set to the default values. The consequence of this functionality is that when switching the model from 1-tissue to 2-tissue and then back, the K_1 and k_2 values will be different due to this conversion process.

4.6.1.7 Model Filtering

The basic model configuration [20] should include all models which may be relevant for a user. Consequently, the model list in the PKIN user interface can still be quite long. Model filtering can be used to quickly tailor it to the current task.

Model Filter Dialog Window

The filter configuration window is opened with the button ▼ next to the model list.
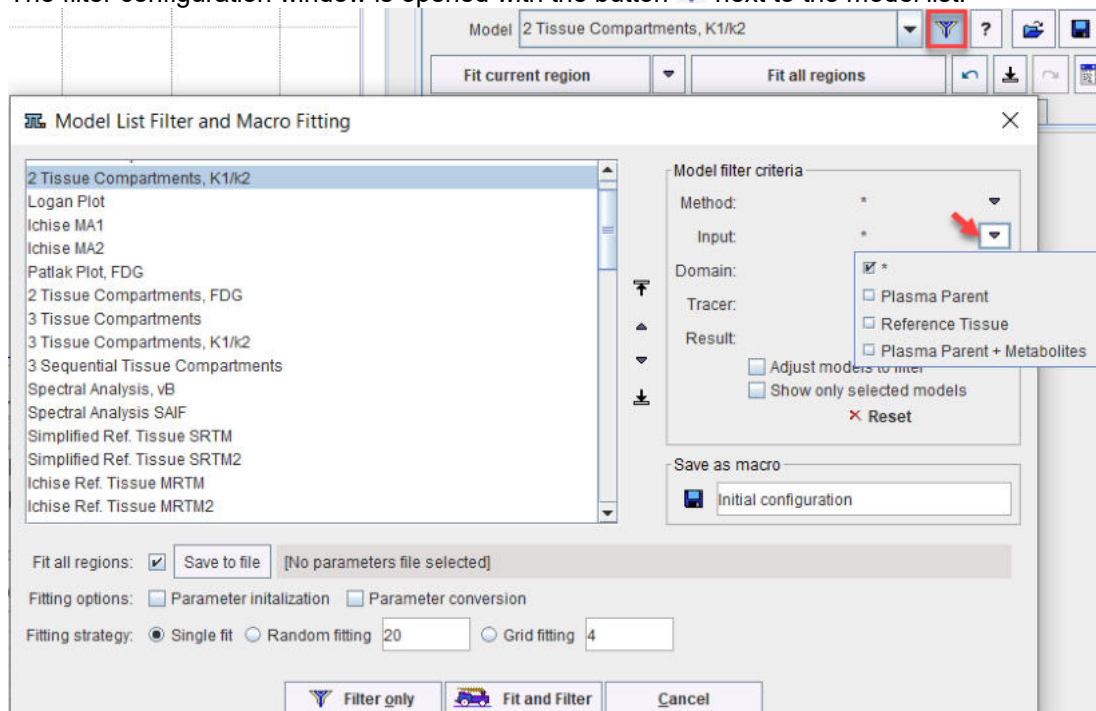
The **Model filter** area has five classifiers which can be enabled

Method	Selections: **Classical PET**, **Compartment Model**, **Graphical Plot**, **Spectral**, **Multilinear**, **Utility**.
Input	Selections: **Plasma Parent** for blood-based models, **Reference Tissue** for reference models, **Plasma Parent + Metabolites** for models with metabolites entering tissue.
Domain	Selections: **Tissue Perfusion**, **Receptor Binding**, **Heart Perfusion**.
Tracer	Selections: **Reversible**, **Trapping**, **FDG**, **NH3**, **H2O**, **Acetate**, **Rb**.

Result	Selections: **Vt**, **BPnd**, **Flux**, **Bmax**.

After selecting one or more filter classifiers the model list in the window is reduced accordingly.

The **Adjust models to filter** flag implements a prior condition on the selected models. Currently, only the **Trapping** has an impact. It causes setting $k_4=0$ in the compartment models.

Show only selected models allows hiding models which satisfy the filter criterion. When closing the filter dialog, only the models selected in the list will be shown.
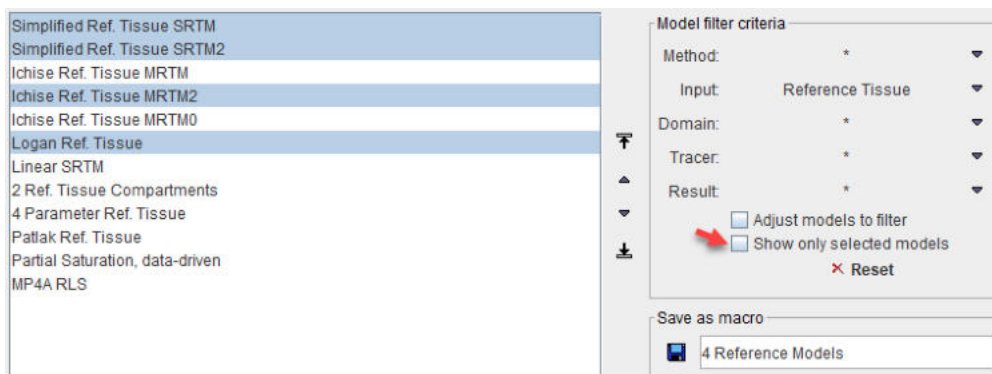
Filter Shortcuts in Taskbar

Note the set of radio buttons in the taskbar to the right for changing the model filter settings quickly.

While **All** shows the unfiltered list, **Bld**, **NoB**, **Ref** and **Irr** restrict the list to blood-based, all but blood-based, reference tissue and irreversible models, respectively.

Filter Activation

When closing the dialog window with **Filter only** and **Fit and Filter**, the entries in the **Model** list are reduced accordingly. Note that filtering is most easily reset by selecting **All** from the taskbar.
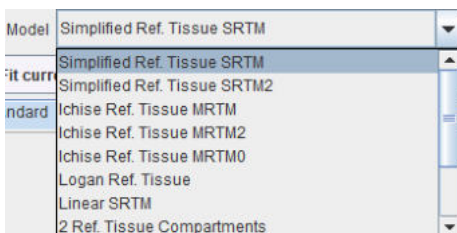
With **Fit and Filter**, the configured <u>Fitting of Multiple Models</u> 61 is additionally executed.

4.6.2   Kinetic Model Fitting

The main elements on the **Tissue** pane for model fitting are:

Fit current region	Starts the process which fits the model curve to the measurements of the selected regional TAC. For compartment models the fit is an iterative optimization, while for some other models only a single calculation may be sufficient.
	Reference model: Fitting the reference region itself is not possible, an information message will be shown.

Fit all regions	Performs fitting for all TACs of the study using their current regional model definitions. Reference model: The reference region itself is skipped without fitting, and the information is stored in the console log.

4.6.2.1   Iterative Fitting Principle

Except for linear and multi-linear regression, minimization of the Chi square [15] expression requires an iterative approach. The procedure starts with a set of initial parameter values, generates the corresponding model curve, calculates the Chi square criterion, and adjusts the model parameters such that Chi square is expected to be reduced. The cycle

- chi square calculation
- parameter adjustment

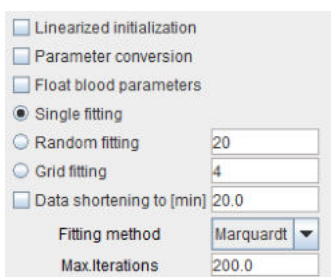is then repeated until a further reduction of Chi square is not any more possible. The final set of parameters upon termination is regarded as the best-fit result. It is not analytically exact and may depend on the initial parameters, on the optimization procedure, and on the termination criterion of the iterations. Fitting is started using the **Fit current region** button.

4.6.2.2   Fitting Options on Extras Panel

The **Extras** pane contains some options which have an impact on model fitting.

Linearized initialization	This configuration is only related to the compartment models and determines which initial values are used for the iterative fitting: ■ Disabled: the user-defined parameters are used. ■ Enabled: an automatic procedure determines initial parameters which should be reasonably close to the solution. This is done by the linear least squares method [123]. Note that the initial values are not shown to the user. However, to see the values, please switch to the linear least squares method and fit.
Parameter conversion	Behavior of the parameters when switching between models [51].
Float blood parameters	If this box it is checked on, *all* parameters of the **Input** curves which have the fit box checked are also included into the set of fitted parameters. This feature has two uses: ■ Fitting the relative time delay between the tissue and the blood data simultaneously with the kinetic rate constants. However, it is easier to directly use the dedicated button [7]. ■ (Rarely) Fitting a shape parameter such as the half-time of a metabolite build-up together with the rate constants as explained below [89]. **Note:** When using **Fit All**, the blood parameters will not be fitted, even if **Fit blood** is enabled.

Single fitting	Default mode of performing one single fit.
Random fitting	This configuration is only related to models which require iterative fitting: ▪ Multiple fits are performed, and the result parameters of the fit with minimal chi squared returned. The fits are started with randomized sets of initial parameters using a uniform distribution with $\pm100\%$ range. Note: If **Parameters initialization** is enabled, randomization uses the automatically determined parameters for the random number generation. ▪ ▪ In case randomized fitting is enabled, the labels of the fitting buttons are adjusted correspondingly. **Note:** The purpose of randomized fitting is to avoid local minima, but there is still a chance that the returned solution may contain unphysiological parameter combinations.
Grid fitting	This configuration is only related to models which require iterative fitting: ▪ Multiple fits are performed, and the result parameters of the fit with minimal chi squared returned. Initial parameter sets are generated by by stepping each parameter in increments between a lower value and an upper value. ▪ The number (n) specified equals the number of distinct values used, so the number of increments is n-1. ▪ The interval of the parameter range to be covered is defined on the Restrictions 51 panel. It is *necessary to adjust these ranges to physiologically reasonable values*, because the default ranges are very wide. ▪ In case grid fitting is enabled, the labels of the fitting buttons are adjusted correspondingly.
Data shortening to	Enables a sequence of fits with a successively shorter data segment to study the parameter sensitivity to acquisition duration.
Fitting method	Selection of the numerical optimization method applied for iterative fitting: ▪ **Marquardt**: Marquardt-Levenberg algorithm [59]. Usually works faster and has the additional advantage that it accumulates information about the covariance matrix. Therefore, an estimate of the standard error can be calculated for the fitted parameters. They are shown as **%SE** (coefficient of variation), ie. as a percentage of the parameter value. ▪ **Powell**: Conjugate direction set method [59]. The iterative optimizations terminate, when no substantial improvement can be found any more, or when the **Max iterations** restriction is hit. **Note:** Several models (linear and multi-linear regression) are not fitted iteratively because they have closed form solutions. In these cases the **Fitting method** settings are not relevant.
Max. iterations	Maximal number of iterations which are allowed in the iterative **Marquardt** and **Powell** fitting.

Note the set of radio buttons in the taskbar to the right for enabling/disabling some of the options quickly.
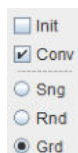
The **Init** and **Conv** boxes correspond to **Linearized initialization** and **Parameter conversion**, respectively. The **Sng**, **Rnd** and **Grd** radio buttons switch between **Single**, **Random** or **Grid** fitting.

4.6.2.3   Residual Weighting

Weighting 15 is used to increase or decrease the influence of certain data samples on the fitting. For instance, initial samples with short acquisition duration and little uptake may be considered less reliable than the samples with longer durations in the presence of high uptake. The weights are multiplied with the squared residuals when calculating the Chi squares criterion.

In PKIN, several different weight definitions are supported. They can be specified on the **Weighting** pane using the list selection with the three entries **Constant weighting**, **Prescribed weighting** and **Calculated weighting**. The contents of the different selections are illustrated in parallel below.
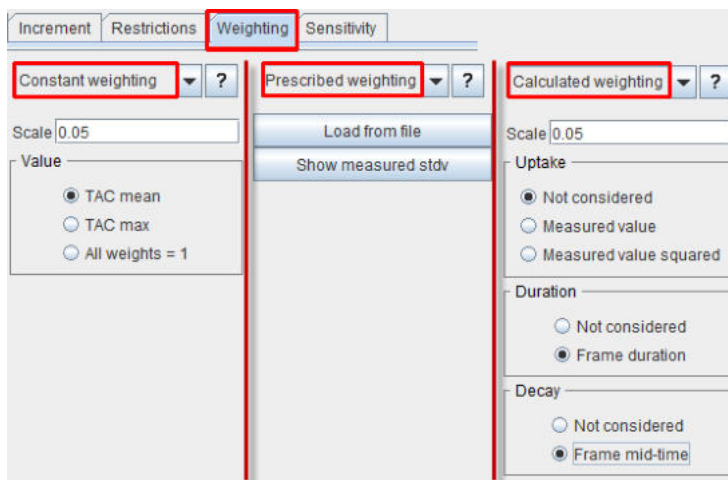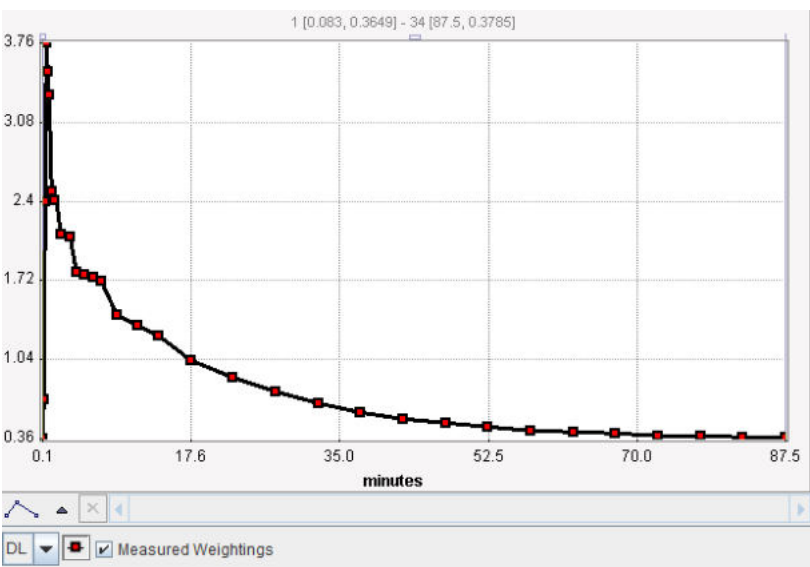
Note that the weights are calculated from the definition of a standard deviation σ_i or the variance σ_i^2 by

$$w_i = \frac{1}{\sigma_i^2}$$

Constant weighting	With constant weighting the same weight is applied to all residuals. Its size can be adjusted by the **Scale** factor and the radio button setting. In the case of **TAC mean** σ_i is obtained as the average of all values in the TAC multiplied by the **Scale** factor. Similarly, with **TAC max** σ_i is obtained as the maximal TAC value multiplied by the **Scale** value. With **All weights = 1** the weights are all set equal to 1 independent of the **Scale** ($\sigma_i = \sigma_i^2 = w_i = 1$). The scale factor doesn't have an impact on the fit result. It is only relevant when the wheiting definition is used for specifying the noise generated for Monte Carlo 84 simulations.
Prescribed weighting	The default behavior of this method is to use the standard deviation of the pixel values in the VOI for calculating the TAC for weighting. This information is automatically available if the TACs have been transferred from the PMOD viewing tool to PKIN, and can be visualized using the button **Show measured stdv** as illustrated below.

This definition can be overwritten by user-defined weights which are to be loaded with the **Load stdv from file** button. Please see below how the file has to be formatted.

| **Calculated weighting**	With this selection the variance is calculated for each TAC value from an equation which may take into account the measured uptake, the radioactive decay, and the duration of the acquisition. The full equation is as follows:

$$\sigma_i^2 = \alpha^2 \frac{C_{PET}(t_i)}{\Delta t_i \, e^{-\lambda t_i}} \qquad \lambda = \frac{\ln 2}{T_{1/2}}$$

It includes a **Scale** factor α, the decay-corrected **Uptake** $C_{PET}(t_i)$ at frame mid-time t_i, the frame **Duration** Δt_i, and the **Decay** constant λ which is obtained from the half-life $T_{1/2}$ of the isotope. If the half-life has not yet been defined, it can be set on the **SUV** panel with the Edit Patient ⌐103⌐ facility.
The settings of the radio buttons have the following effect on the equation above for calculating σ_i^2:

- **Uptake**:
  Not considered: $C_{PET}(t_i)$ is replaced by 1.
  Measured value: $C_{PET}(t_i)$ is used, corresponding to *Poisson weighting*. The effect is that more emphasis is given on low-uptake values than on high-uptake values. This may be helpful for example if the fit seems to not account enough for the tail of a decreasing function such as the input curve.
  Measured value squared: $C_{PET}(t_i)$ is replaced by $C_{PET}^2(t_i)$, corresponding to *Relative weighting*. With this option the influence of the uptake is further increased. It should be used with care because by squaring small (initial) uptake values ($\ll 1$) very small variances are generated which transform into heavy weighting. As a consequence, a few small uptake values may have excessive impact on the fit.

- **Duration**:
  Not considered: Δt_i is replaced by 1.
  Measured value: The individual frame durations Δt_i are used, so that longer acquisitions are considered more reliable.

- **Decay**:
  Not considered: $e^{-\lambda t_i}$ is replaced by 1.

	Frame mid-time: $e^{-\lambda t_i}$ is used, so that earlier acquisitions are considered more reliable.
	Note: As a corrective measure, very small standard deviations of the first 1/3 data points (likely to have low uptake) are adapted to provide reasonable weights as follows: If the stdv is smaller than the average stdv and smaller than 50% of its successor, it is replaced by the stdv of the successor.

Whenever the configuration is changed, the standard deviation σ_i is calculated and plotted as an error bar around the measurements. This gives the user a visual feedback as a help in judging the adequacy of the specified weighting.
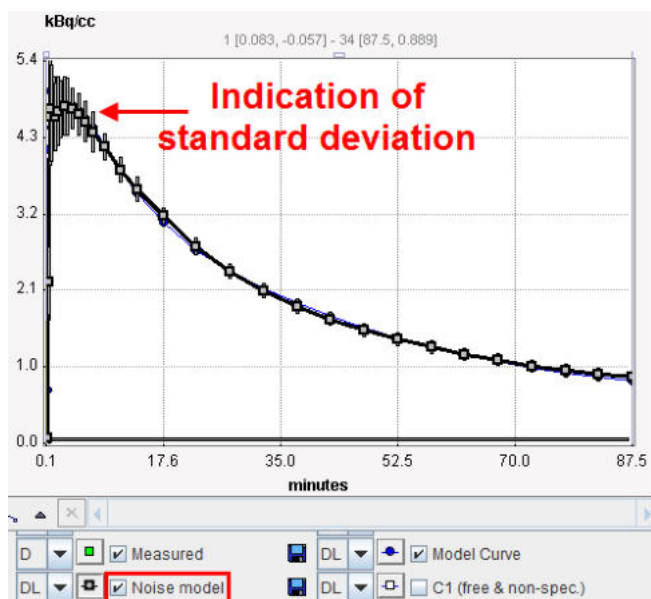
Loading Externally Defined Weights

Some users might want to implement their own residual weighting schemes. To this end they should calculate the standard deviations σ_i for the different acquisition frames from which the weights will be calculated according to

$$w_i = \frac{1}{\sigma_i^2}$$

The σ_i should be prepared in a tab-delimited text file of the following form:

t[seconds]	standard-dev[kBq/cc]
10	0.10300076
30	0.01717448
50	0.01195735
70	0.01010257
etc	...

The header line is required. The first column represents the frame mid-times (although the values are not interpreted), and the second column the standard deviations in appropriate units. The number of entries must be equal to the number of acquisitions, and the columns separated by spaces or tabs. For example, such a file can be prepared in MS Excel and then saved as a text file with tab delineation.

This definition can be loaded by the **Load stdv from file** button available with **Prescribed weighting**.

Display of the Residuals

The curve area with the residuals per default shows the weighted residuals, that is the difference between the measurement and the model curve divided by the standard deviation.

$$r_i = \frac{[C_{PET}(t_i) - C_{Model}(t_i)]}{\sigma_i}$$

However, the raw residuals can also available. The context menu as illustrated below (right mouse click into the curve area) can be employed for showing/hiding the curve controls, which allow changing the displayed information.
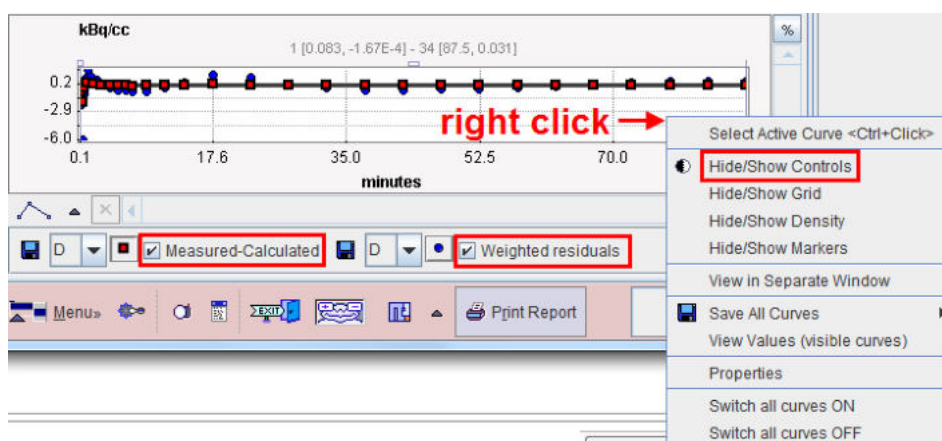
Use of the Weights in Monte Carlo Simulations

Monte Carlo simulations require the generation of noise which is defined by a distribution type as well as its deviation characteristics. Assuming that the weights specification corresponds to the standard deviation of the measurement noise, the regional weighting specification is used in the Monte Carlo noise generation together with the distribution type. Note that the **Scale** factor has no impact on fitting, but that it is highly relevant in Monte Carlo simulations.

4.6.2.4   Model Fitting History

The system maintains a history of model configurations for each region. All operations, which change the model configuration result in a new entry in the history list. The history is saved within a .km file and will be continued after reloading the data.

The history functionality is accessible by the user interface elements right to the model configuration
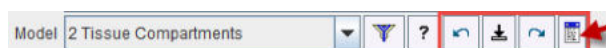
↰	Switches to the previous model configuration in the history list.
⤓	Appends the current model configuration to the list.
↱	Switches to the following model configuration in the list.
▦	Shows the history window.

CAUTION: This history mechanism does not account for changes in the configuration of the blood-related models, except for the blood delay. However, it includes the definition of the residual weighting, the valid points, and the tissue TAC values.

History Window (PKIN Parameters Explorer)

The history list is shown in the **PKIN parameters explorer** window as illustrated below. It has exactly the same organization as the [window for comparing all regional results](#) 75, except that only the information of the current window is available. Please refer to the description [there](#) 75 for more details.
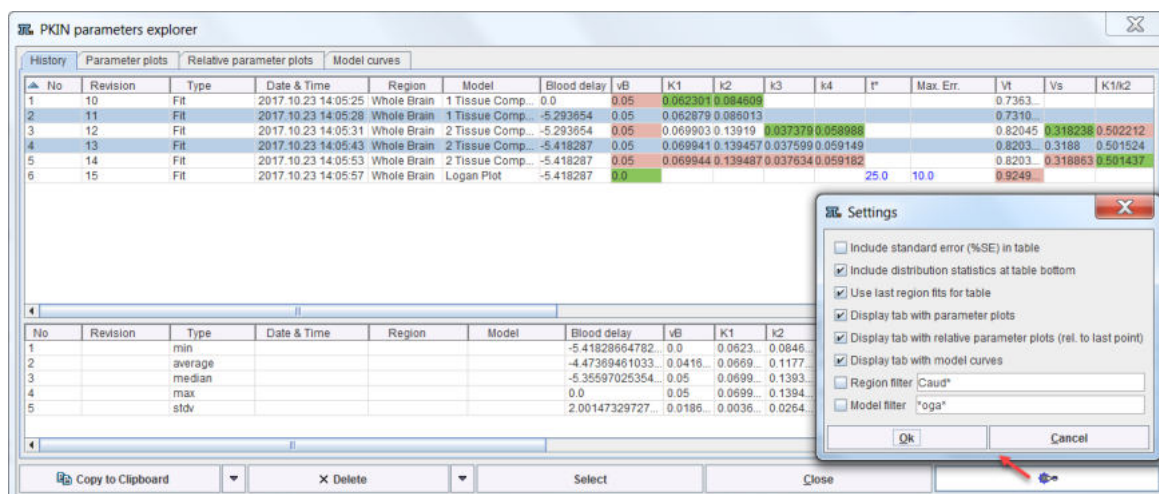
The upper part of the **History** panel lists the model configurations in rows. The initial columns are descriptive, followed by the actual parameters. Note that the parameters are sorted into appropriate columns even across different model types. For instance, **Vt** resulting from all compartment models as well as the Logan plot appears in the same column so that the values can easily can be compared. The user can change the order of the columns by dragging the column headers left or right. The smallest value per column is encoded in green, the largest in red. Columns having a constant value are encoded in blue. The **No** column refers to the chronology of list entry. **Revision** serves for grouping results from a certain task such as the [parameter sensitivity analysis](#) 81. **Type** indicates by what process the configuration was added. The list can be flexibly sorted by clicking on the column headers.

To restore a model configuration double-click the list entry or mark it in the list and activate **Select**. Model configurations can be removed by selecting them in the list and activating **Delete**. The **Clear All** button
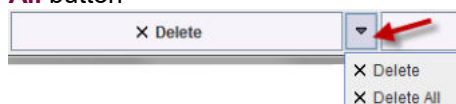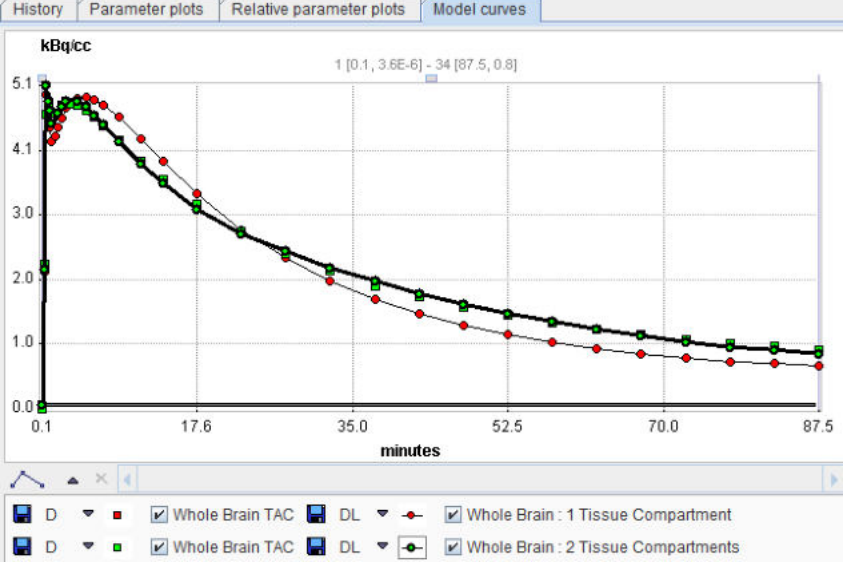
allows resetting the history completely.

Optional Elements

The window has some configuration **Settings** which can be opened as illustrated above. The elements to be changed are:

Include standard error (%SE) in table	Include a column with the % standard error for each parameter.
Include distribution statistics at table bottom	Enable the lower area showing the **min**, **average**, **median**, **max** and **stdv** per column.
Use last region fits for table	Not relevant for the fitting history of a single region.
Display tab with parameter plots	Shows an additional panel for the visualizing the parameters of the selected **History** rows as curves.

Display tab with relative parameter plots	As above, but with normalization to the last value.
Display tab with model curves	Shows an additional panel for concurrently [visualizing the model curves of the rows selected on the History tab](#) 77.
Region filter	Not applicable here.
Model filter	For filtering the entries listed. With ***Comp***, for instance, only compartment model results will be listed.

Saving Options

There are different types for saving the parameters from the fitting history using selection in the lower left.
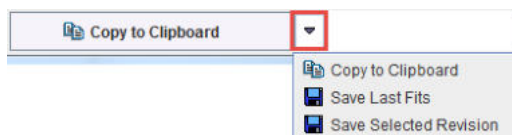
Copy to Clipboard copies the entire window contents, so that it can be pasted into another application for further analysis. **Save Last Fits** saves the latest fit results from all regions into a .kinPar file. **Save Selected Revision** saves the fits from all regions with the currently selected **Revision** number to a .kinPar file and can be used for exporting the results from a [duration sensitivity analysis](#) 81.

4.6.2.5   Fitting Multiple Models

Using the [model filtering](#) 52 approach multiple models can sequentially be fitted to a regional TAC, whereby the results are recorded using the [history](#) 59 mechanism and can easily be inspected.

To specify the fitted models please open the filter dialog window, optionally specify a **Model filter** to reduce the number of models, and select the models of interest as illustrated.
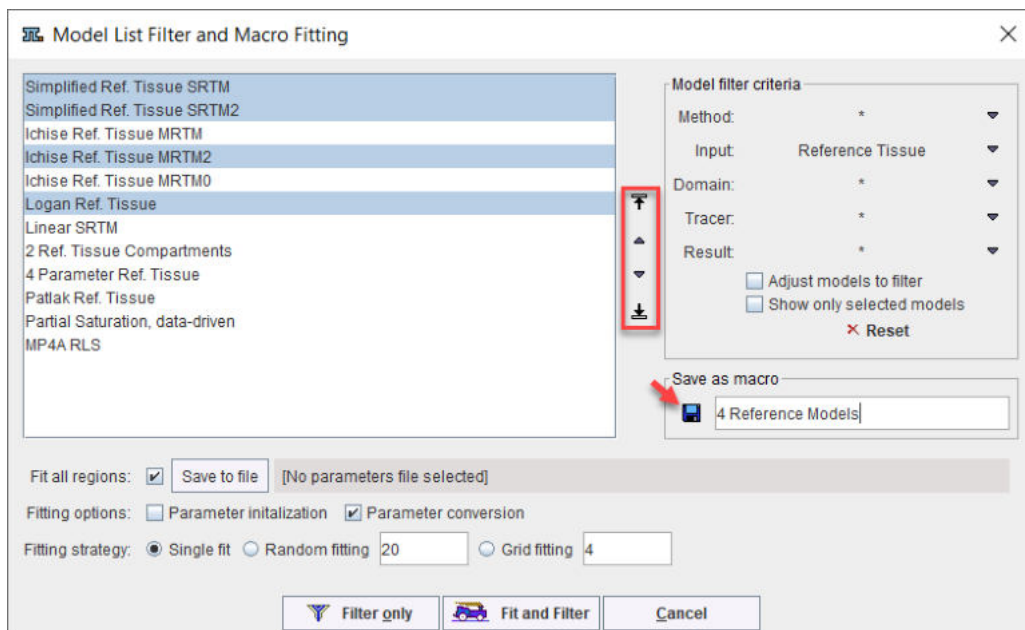
Fitting all Regions

The multi-model fit can be applied to all regions by enabling the **Fit all regions** box. In this case, as a convenience for the results comparison, the parameters of all model fits in all regions can be directed to a kinetic parameter file (**.kinPar**). Such a file can easily be opened in programs such as MS Excel, but it can also be opened in the aggregation 98 window for extracting the information of interest.

Initial Parameters

The models will be fitted according to their order in the list. The initial parameters and the fitting flags will correspond to the model default, if the model has not yet been fitted for the regional TAC. Otherwise, the last used parameter configuration will be used (per region) as the starting condition.

Note that configurations on the **Extras** 54 pane are mirrored in the **Fitting options** section. The mainly relevant ones are **Parameter initialization** to estimate initial parameters of compartment models by the linear least squares method, and **Parameter conversion** which directs the program to apply built-in rules when switching to the next model. This behavior is required for the model set illustrated above, because **SRTM2**, **MRTM2** and **Logan Reference** require the specification of a k_2' input parameter. With **Parameter conversion** on, SRTM2, MRTM2 and Logan Reference will inherit the estimated k_2' from the immediately prior reference tissue model. This can easily be verified by opening the model fitting history.

Fitting Strategy

The different approaches on the **Extras** 54 pane for reducing the dependency on the initial parameters can be selected in the **Fitting strategy** section.

Start Fitting

The **Fit and Filter** button starts the configured model fits. Note that depending on the data and the setting of **Fit all regions**, **Random fitting**, and **Grid fitting,** processing can take a while. The results will be recorded in a parameter file, if configured, and in the regional histories.

4.6.2.6   Fitting Macros

Macros allow fitting a sequence of models to a data set.

Fitting Macro Creation

The sequence of models to be fitted can be defined via the Model Filtering 52 dialog window.
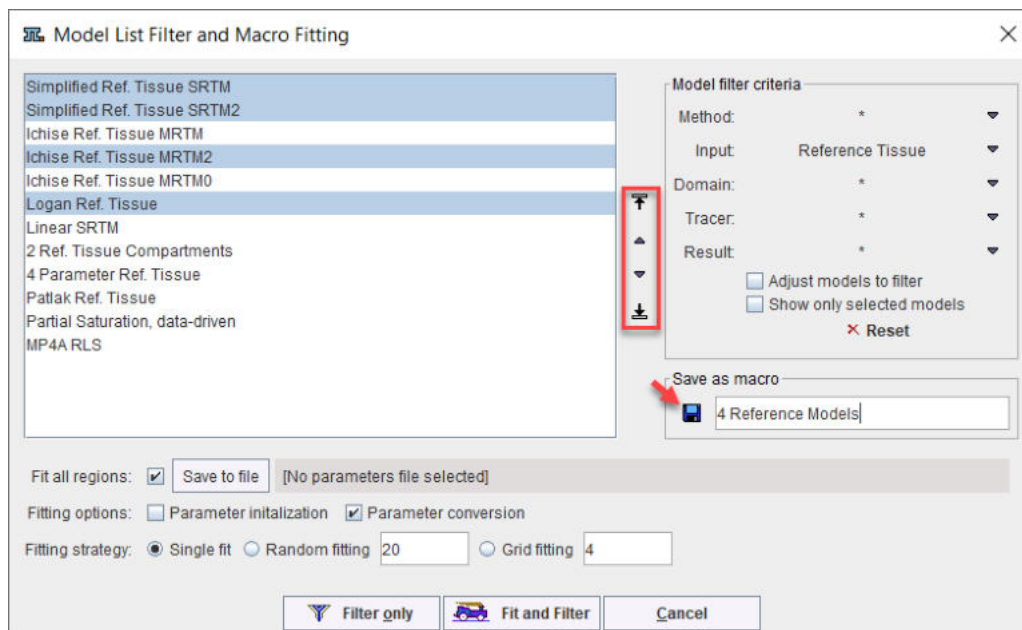
Simply select the models in the list, order them using the indicated arrows, configure all the options described in Fitting Multiple Models 61, and activate **Save as macro** to save it to a database or the file system. For most convenient access it is recommended saving them to the sub-folder *resources\pkin\macros* in the PMOD installation directory.

Applying a Macro

Once macros have been prepared, they can be activated from the lateral taskbar.
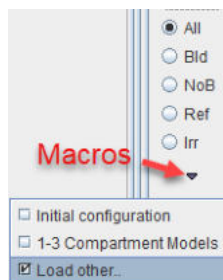
If they were saved to *resources\pkin\macros* they directly appear in the list. Otherwise, they have to be selected via **Load other** from the database or the file system.

Loading the macro has the effect that the Model Filtering 52 dialog window is opened with all settings. Fitting can the be started with the **Fit and Filter** button.
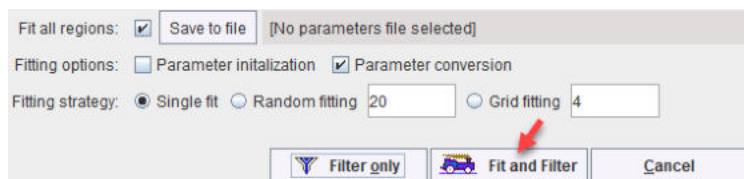
4.6.2.7   Fitting Problems

In the case of a failed fit it is worthwhile to check the console output. For example, the output text reproduced below clearly indicates that the 4th fit parameter caused a problem.

```
Singular Matrix-2
covar[1][1] = 2.1652603147908747E-6
covar[1][2] = -5.120936302955895E-4
covar[1][3] = 2.862241687078937E-7
covar[1][4] = 0.0
covar[2][1] = -5.120936302955895E-4
covar[2][2] = 0.3918087002588389
covar[2][3] = -2.0406232308544742E-4
covar[2][4] = 0.0
covar[3][1] = 2.862241687078937E-7
covar[3][2] = -2.0406232308544742E-4
covar[3][3] = 1.4044964781403112E-7
covar[3][4] = 0.0
covar[4][1] = 0.0
covar[4][2] = 0.0
covar[4][3] = 0.0
covar[4][4] = 0.0
```

Such problems might be caused by initial values very close to parameter restrictions.

4.7   Coupled Fitting for Improving Parameter Estimates

In some situations the introduction of prior (physiologic) knowledge can help improving the stability of model fitting.

For instance, in receptor experiments it may be adequate to assume that the distribution volume (K_1/k_2) of the non-displaceable compartment and/or the dissociation rate from specific binding sites (k_4) are equal in certain tissues of the brain. Hence, a simultaneous fit of selected regional TACs of a scan can be performed which finds separate K_1 and k_3 values per TAC, but which delivers a K_1/k_2 and k_4 which is common for all TACs. As an example, Sanabria-Bohorquez et al [1] have used a coupled k_4 for solving the problem of unstable fits. In PKIN this type of fitting is called **Coupled Fitting**.

Another valuable application of **Coupled Fitting** is determination of k_2' for Reference Tissue models. k_2' denotes clearance of the tracer from the reference tissue. Hence, it is natural to enforce a common k_2' as physiologic restriction when fitting the TACs from different target tissues as explained <u>below</u> .

The concept can be extended to the fitting of data from different scans of the same subject, for instance test/retest scans which are replicate measurements under the same conditions and where the parameters should be very similar if the regions are consistently outlined. Plisson et al. [2] have applied simultaneous fitting with the data of pigs which were studied in a baseline condition and with different degrees of receptor blocking by cold compound. By applying the simultaneous fitting, they were able to get stable estimates, which was not possible with independent fitting. In PKIN this type of fitting is called **Coupled Studies Fitting** and distinguishes two variants of coupling. GLOBAL coupling of a parameter results in single value which is common for all fitted TACs. **REGIONAL** coupling of a parameter results in common value per region. For instance, if k_3 is defined as a parameter with **REGIONAL** coupling and the coupled regions from two scans are *caudate*, *putamen* and *frontal*, a different k_3 estimate will result for each of these three regions, but each of them is common across the TACs of the two scans.

The requirements for coupled fitting in PKIN are:

▪ The same model applies to the TACs of several tissue regions (Note: not all models may be coupled, only models with iterative fitting).

- There exists one or more parameters in the model configuration which can be assumed to have a common value for different TACs.

References

1. Sanabria-Bohorquez SM, Hamill TG, Goffin K, De Lepeleire I, Bormans G, Burns HD, Van Laere K. Kinetic analysis of the cannabinoid-1 receptor PET tracer [(18)F]MK-9470 in human brain. Eur J Nucl Med Mol Imaging. 2010;37(5):920-33. DOI

2. Plisson C, Gunn RN, Cunningham VJ, Bender D, Salinas CA, Medhurst AD, Roberts JC, Laruelle M, Gee AD. 11C-GSK189254: a selective radioligand for in vivo central nervous system imaging of histamine H3 receptors by PET. J Nucl Med. 2009;50(12):2064-72. DOI

4.7.1   Common Parameters across Regional TACs of a Single Study

Coupled Fitting to Estimate and Apply a Common k2'

The following sequence of steps is recommended for coupled fitting. The example illustrates fitting of a common k_2' using the SRTM2 [154] model. It is equivalent to the SRTM [153] model, but due to a different arrangement of the equations k_2' appears as a fitting parameter which allows using coupled fitting.

1. Select a regional TAC with good signal.

2. Switch to the model (**SRTM2**) to be applied in coupled fitting.

3. Fit the TAC with **Fit current region** and propagate the model to all other regions with the button **Model & Par**.
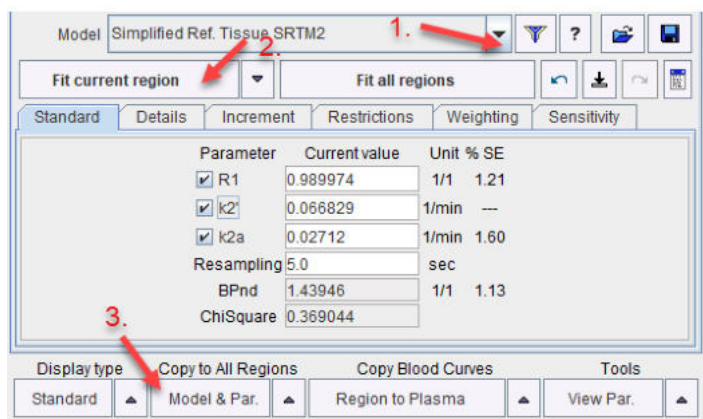
4. Use **Fit all regions** to establish reasonable starting values for all TACs.

5. On the **Coupled** panel, enable the parameter(s) which are to be treated as common, and enable all target regions which should be fitted together. Note that the disabled parameters will

be estimated per region.
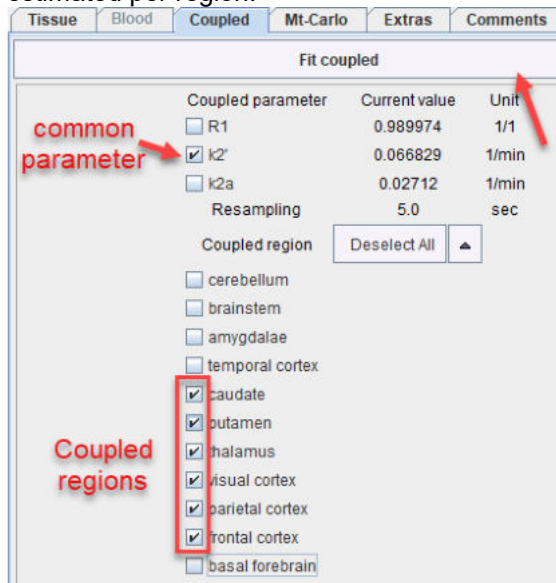
6. Start processing with **Fit coupled**. Coupled fitting may take significant processing time. Thus the **Batch mode** facility may be a helpful option to run such jobs at less busy times.

7. On the **Tissue** panel, switch to one of the coupled regions. The k_2' shown there is the common estimate. This can be verified by opening the parameter explorer with the **View Par** button.
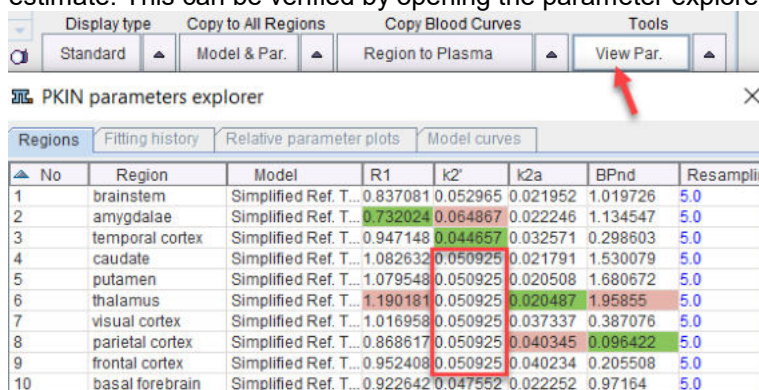
8. To use the common parameters for the fitting in all regions select one of the coupled regions. The **Standard** panel shows the result of the coupled fit including the estimated values of the common parameters. Note their standard error **%SE** which should be decreased compared with individual fits. Disable the fit box of the common parameter(s) and propagate this configuration to all regions with the **Model & Par** button. Apply **Fit all regions** to re-fit the model with the fixed common parameters which are now also enforced in all regions.
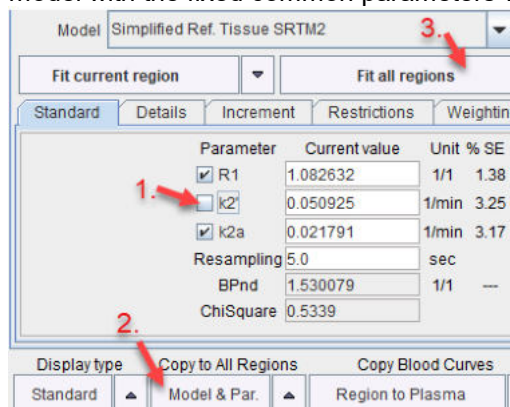
Coupled Fitting to Improve Robustness of 2-Tissue Compartment Model (2TCM) Fitting

It is often difficult to get robust estimates for k_3 and k_4 with 2TCM fitting. In order to support parameter coupling, an alternative formulation of the 2TCM is supported which uses K_1/k_2 (distribution volume of non-displaceable compartment) as fitting parameter instead of k_2.

To perform 2TCM coupled fitting proceed similarly as described above:

1. Select a regional TAC with good signal.

2. Switch to the model (**2 Tissue Compartments, K1/k2**) to be applied in coupled fitting.
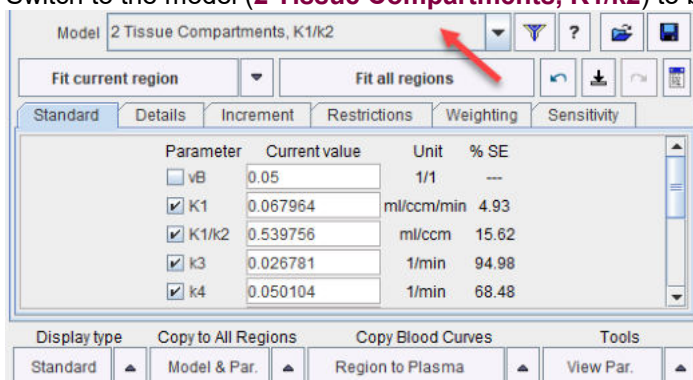
3. Fit the TAC with **Fit current region** and propagate the model to all other regions with **Model & Par.**

4. **Fit all regions** to establish reasonable starting values for all TACs.

5. On the **Coupled** panel, enable the parameter(s) which are to be treated as common, and enable all target regions which should be fitted together. Note that the disabled parameters will be estimated per region.
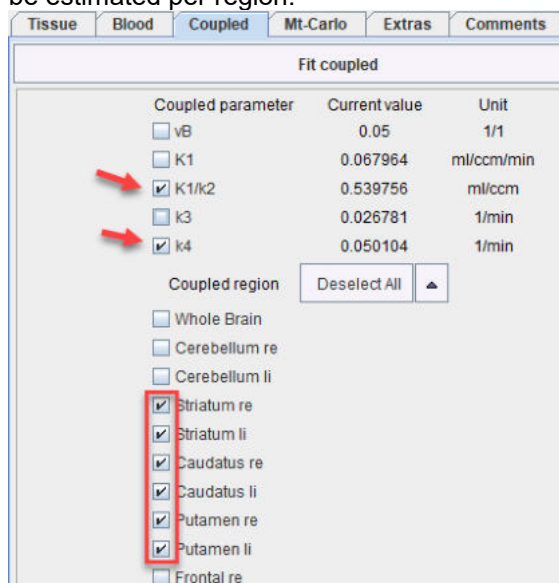

6. Start processing with **Fit coupled**.

7. To use the common parameters for fitting all regions select one of the coupled regions. The **Standard** panel shows the result of the coupled fit with the estimated values of the common parameters. Disable the fit box of the common parameter(s) and propagate this configuration to all regions with the **Model & Par** button. Apply **Fit all regions** to re-fit the model with the fixed common parameters which are now also enforced in regions which have not been included in coupling.

Coupled Fitting Procedure

The coupled fitting process works as follows:

- A global target curve is created by stacking the TACs of the checked regions (valid points only).

- The corresponding weights are calculated according to the weighting configuration for each TAC.

- A table of fitted parameters is formed by entering the common parameters once and adding all the other fit enabled parameters in the coupled regions. The initial values of common parameters are taken from the first checked region, for the other parameters from the individual regional models. If **Fit blood parameters** is enabled on the **Fitting** pane, the fit-enabled parameters of the blood curves are also taken into account. As a convenience there is a button **Fit coupled and delay**
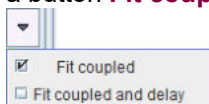
to estimate a blood delay which considers the information from all coupled regions.

- The optimizer calculates the model curve in all checked regions, creates the global result curve corresponding to the target curve, weighs all the residuals and forms the global sum of squares as the figure of merit. The parameters are adjusted until the cost function has been minimized, and the resulting parameters are copied are copied back to the individual models.

4.7.2 Common Parameters across Regional TACs from Different Studies

Preparations

For a simultaneous fit of TACs from multiple studies the user first has to

- load all of the data sets so that they are available on different tabs;

- ensure that all of the TACs to be coupled have the same compartment model configuration and the same residual weighting;

- ensure that all model parameters have reasonable initial values by either fitting the models, or propagating a model configuration.

The coupling is performed on a separate dialog window which can be opened from the **Kinetic** menu with the **Coupled Studies Dialog** entry.

Study and Model Selection

The dialog window opens on the first tab **Study/Model selection** containing three sections.
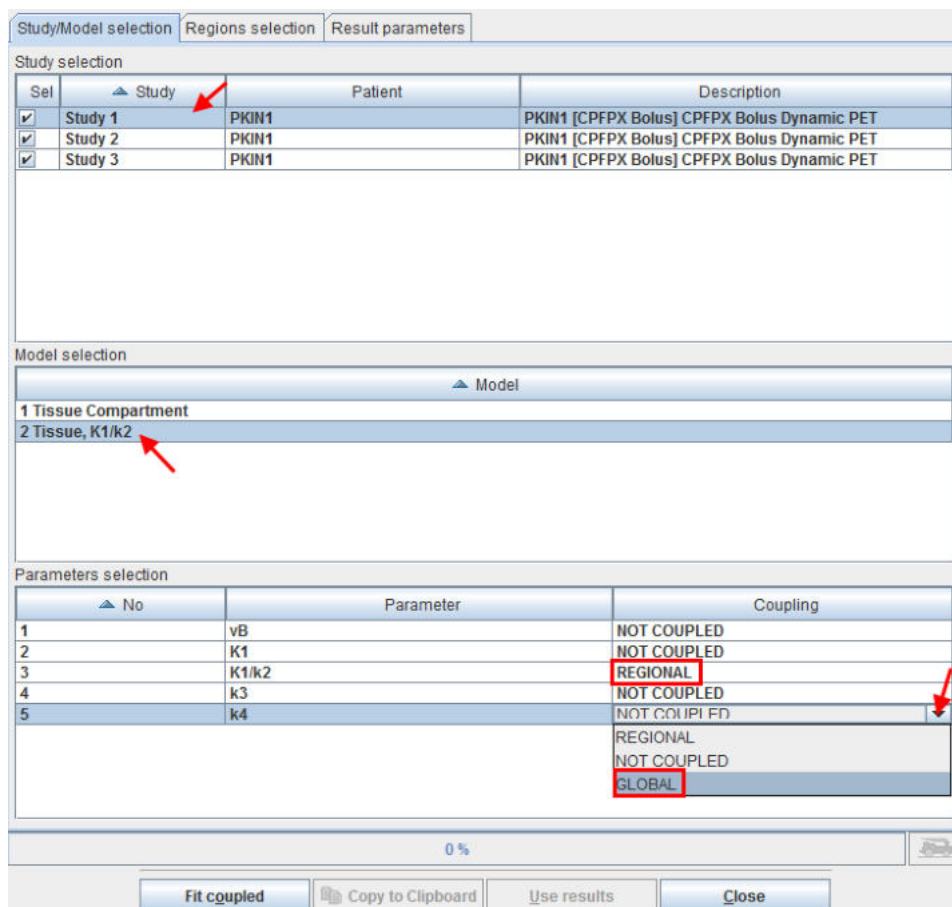
The **Study selection** lists all open data sets. As soon as one of them is selected in the list, the **Model selection** list is updated, showing the different models which are used for the TACs of the study. In the example shown above one of the regions (which is not used four coupling) uses a **1 Tissue Compartment** model, whereas the regions intended for coupling use the **2 Tissue K1/k2** model.

After selecting the appropriate model, the **Parameters selection** list is updated showing all parameters of the model together with a **Coupling** selection. A parameter can have one out of three configurations:

- **NOT COUPLED**: The parameter will be individually fitted in the different regional models or kept fix depending on the state of the individual fit box.

- **REGIONAL**: The parameter will be coupled among all regions with the same name. For instance, the parameter will have a common value for all *caudate* regions, a different common one for all *putamen* regions, etc. Note that with this configuration the state of the individual parameter fit boxes is not relevant, the parameter will be modified in all coupled regions.

- **GLOBAL**: The parameter will be coupled among all coupled regions independent of their name. For instance, the parameter will have the same common value among all *caudate*, *putamen*, etc regions. Note that with this configuration the states of the individual parameter fit boxes is not relevant, the parameter will be modified in all coupled regions.

Regions Selection and Fitting

The next step is defining the TACs included in the coupled fit on the **Regions selection** pane as illustrated below.
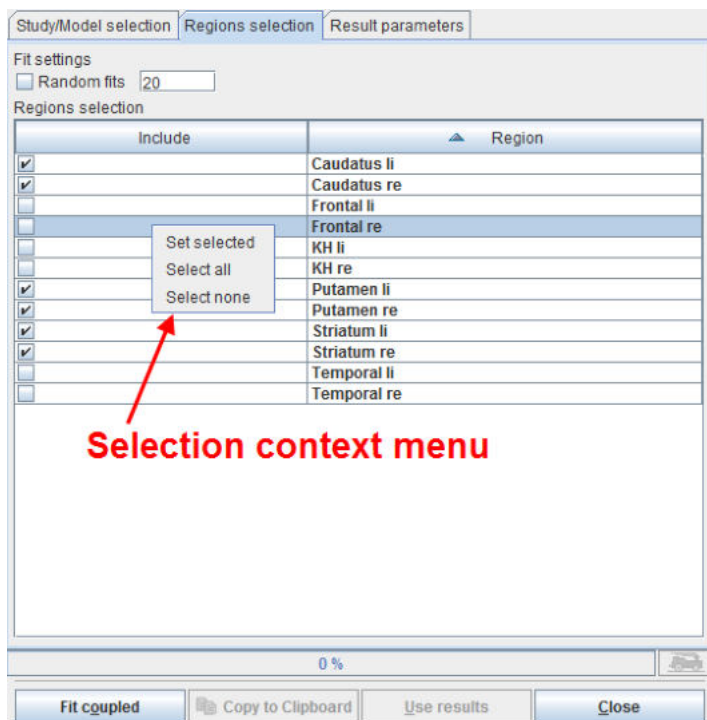
The list contains all regions which are defined in the coupled studies with *exactly the same names*. Initially all regions are selected for inclusion. Regions can selectively be unselected by checking their box. When working with large number of regions (e.g. from atlas definitions) the context menu may be helpful which can be opened by right clicking into the list. It contains **Select all** and **Select none** for quickly selecting or de-selecting all regions, respectively.

Coupled fitting is started using the **Fit coupled** button and proceeds as follows:

▪ A global target curve is created by stacking the TACs of all coupled regions from the selected studies (valid points only).

▪ The corresponding weights are calculated according to the weighting configuration for each TAC.

▪ A table of fitted parameters is formed by entering the **GLOBAL** parameters once, the **REGIONAL** parameters once per region, and adding all the other fit enabled parameters in the coupled regions. The initial values of common parameters are taken from the first study, for the other parameters from the individual regional models. Note that **Fit blood parameters** has no impact on fitting, all the parameters of the blood curves remain fixed.

The optimizer calculates all model curves, creates the global result curve corresponding to the target curve, weighs all the residuals and forms the global sum of squares as the figure of merit. The parameters are adjusted until the cost function has been minimized. If the box **Random Fits** is checked, the fitting will be repeated as many times as specified with randomly changed starting parameters and the result with minimal global chi square returned.

Result Parameters

After the coupled fit has completed the resulting parameters in the coupled regions are listed on the **Result parameters** pane which is immediately shown.

Note in the example above that the **REGIONAL** parameter K_1/k_2 has the same value in all regions with the same name, whereas the **GLOBAL** parameter k_4 has the same value in all regions.

The results can be prepared for use in another program such as MS Excel with the **Copy to Clipboard** button. The **Use results** button transfers the result parameters together with their standard errors to the individual models and closes the dialog window, whereas the results are discarded by the **Close** button.

4.8   Blood Delay Fitting

The timing of the tissue and the blood data should be synchronized to a common clock. Nevertheless, there may be an inherent shift of the blood activity curves relative to the tissue activity curves because of the arrival time difference of the blood in the target tissue and at the sampling location. For brain PET scans with radial artery blood sampling the tracer will appear later in the blood samples than in the brain. This delay is even prolonged if the blood samples are not taken directly with a syringe, but via a catheter which adds additional pathlength as required by online blood sampling devices.

Such a relative delay of the blood samples is accounted for by the **Delay** parameter of the blood models 43. Positive delays represent delayed blood information and hence shift the blood curves to earlier times (to the left). While both the whole-blood and the plasma model include a separate **Delay** parameter, it is reasonable to assume a common delay since the plasma activity is derived from whole-blood. Such a common delay can be fitted together with the kinetic parameters of the tissue model as described below.

Delay Fitting with Single Tissue TAC

The **Tissue** tab features a dedicated **Fit region and blood delay** button. It is hidden underneath the **Fit current region** button and can be activated as illustrated below.
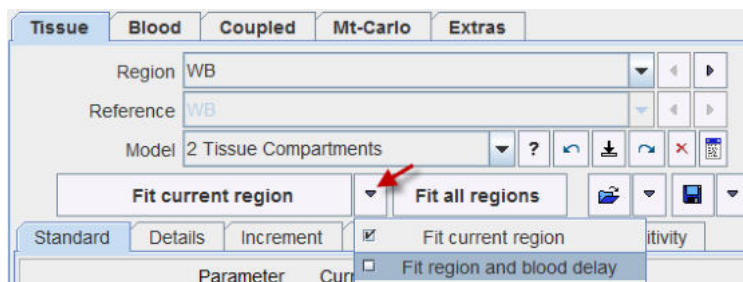
When it is activated, the following actions are performed:

- The state of the fit flags of the **Whole blood** and **Plasma** models is saved.

- The fit flag of the **Delay** is enabled, and all other fit flags disabled.

- A fit of the tissue model is performed, whereby the **Delay** (common to plasma and whole blood) is also optimized.

- The state of the fit flags of the **Whole blood** and **Plasma** models is restored.

- The estimated **Delay** can be inspected on the **Blood** tab or in the model history.

The illustration below shows a history of the outcome when fitting a 1- and 2-Tissue compartment model to the WB TAC including the delay.

▲ No	Type	Region...	Model	Blood delay	vB	K1	k2	k3	k4	Vt
1	Fit	WB	1 Tissue Compartment	0.0	0.05	0.061412	0.083889			0.7320
2	Fit	WB	1 Tissue Compartment	5.138192	0.05	0.062031	0.085247			0.7276
3	Fit	WB	2 Tissue Compartments	5.412845	0.05	0.069059	0.139496	0.0381970	0.058912	0.8160

It is notable that the optimal delay depends on the fitted model, and it will also depend on the selected regional TAC. When using a single TAC it is recommended using the signal from a relatively large VOI, for instance the whole brain, and then keep the delay fixed.

> **Note:**
> 1. A change of the blood **Delay** affects the model curve of all regions and therefore requires re-fitting all regional models.
> 2. When using **Fit All**, the blood parameters will not be fitted, even if **Fit blood** is enabled on the **Extras** panel.

Delay Fitting with Multiple Tissue TACs

An alternative to using a single representative tissue is the use of coupled fitting 65 for the determination of a blood delay which is optimal with respect to tracer appearance in several regions. In the example below 8 regions are selected on the **Coupled** pane all of which have a 2-tissue compartment model configured.
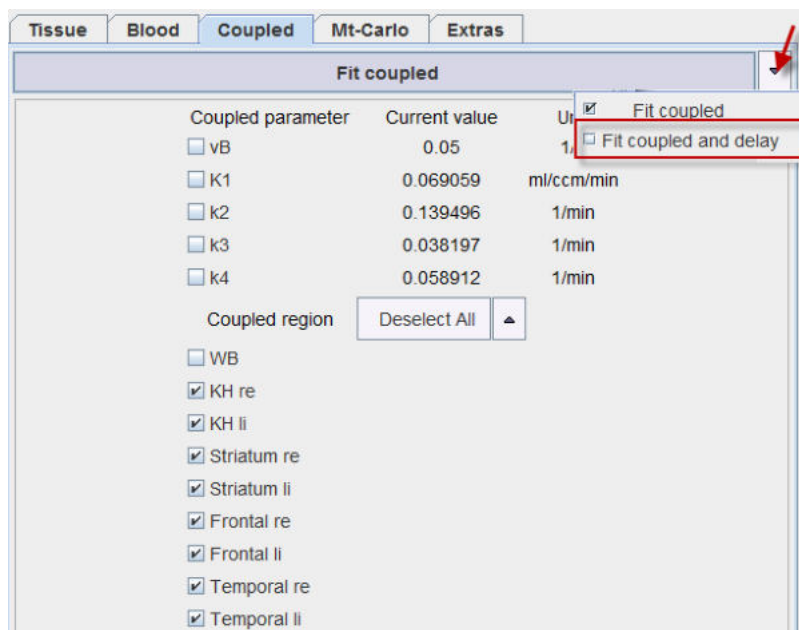
Fitting of the common delay is started using the **Fit coupled and delay** button which is hidden under the **Fit coupled** button. The procedure will fit all 8 compartment models while at the same time optimizing the blood timing.

4.9   Assessing Fit Results

The physiologic behavior of PET tracers is usually quite complex. A comprehensive model accurately describing its kinetics therefore requires many compartments and exchange parameters. However, as the PET signal is limited in quality and information, the model must be simplified to a degree that only a few parameters remain. When estimating a model with many parameters, the variance of the parameter estimates tends to be very high, so that a reliable interpretation of the results becomes impossible. A simplified model with fewer parameters will provide more precise results, but these parameters may be biased. Therefore, the optimal trade-off between bias and uncertainty has to be sought by testing models of decreasing complexity.

After every model fit detailed information about the parameter estimates and the goodness-of-fit is available on the **Details** tab.

Parameter Standard Error

Nonlinear regression using the Levenberg-Marquardt optimization reports a standard error (SE) for each fitted parameter value. The SE is calculated by multiplying the diagonal elements of the covariance matrix obtained by the fit with Chi Square and taking the square root. Note that SE is displayed as % of the actual parameter value.

Calculation of the macroparameter SE involves the covariance matrix and the partial derivatives at the solution. Example of the SE calculation for Vs of the 2-Tissue compartment model (Vs=K1k3/k2k4):

```
if (k2k4 > 0)    { // Calculation of the the partial derivatives (pder) of Vs at the solution
    pder[K1_IND] = k3 / k2k4;
    pder[K2_IND] = -K1 * k3 / (k2 * k2k4);
    pder[K3_IND] = K1 / k2k4;
    pder[K4_IND] = -K1 * k3 / (k4 * k2k4);
            variance = varianceFromModelCovar(pder, covar); // matrix multiplication:
pder_transverse*covar*pder
    SE = sqrt(variance*chiSqr);
}
```

The reason why the SE of a macroparameter can be lower than that of the parameters involved in the calculation is that the parameters are correlated.

Parameter Confidence Intervals

If the inherent fitting assumptions are true, a 95% confidence interval can be approximated by the result parameter plus/minus two standard errors. This confidence interval is displayed for each fitted parameter (**Conf.low**, **Conf.high**).

There will be a 95% chance that the confidence interval contains the true parameter value. A sufficiently narrow confidence interval indicates that the parameter could be determined with a reasonable certainty, whereas a wide interval makes it necessary to revise the configuration of the used model, or look for a more appropriate model.

Goodness-of-Fit

The following measures are defined which allow a direct or indirect assessment of the goodness-of-fit:

DOF	**Degrees of freedom** defined as the number of valid measurements minus the number of fitted parameters.
SumSquared	Sum of squared (unweighted) residuals.
ChiSquare	**Reduced Chi square**. Sum of squared, weighted residuals, divided by the degrees of freedom. The reduced chi-square provides a useful measure of goodness-of-fit. If the model describes the measured data, the reduced chi-square will mostly represent the variance of the data and will be close to 1.0 (when weighting is appropriate).
AIC	**Akaike Information Criterion**. The AIC methodology attempts to find the model that best explains the data with a minimum of free parameters. The AIC is calculated with the second order correction for small sample size (<40). The preferred model is the one with the lowest AIC value.
SC	**Schwartz Criterion**, also called Bayesian Information Criterion (BIC). The preferred model is the one with the lowest SC value.
MSC	Another criterion used in the *Scientist* Software (MicroMath, Saint Louis, Missouri USA) is the **Model Selection Criterion.** The preferred model is the one with the highest MSC value.

R2	There is also a measure of the goodness-of-fit, the **coefficient of determinationR2**, a number between 0 and 1. A value of 0 means that the fit is not better than a horizontal line through the mean of all measurements, whereas a value of 1 means that all measurements lie exactly on the curve. High R^2 values indicate that the model curve is close to the measurement.
Sy.x	Another information about the residuals is provided by the **root mean square value Sy,x**. It is defined as the standard deviation of the residuals and can be used to generate synthetic measurements in Monte Carlo simulations, provided all measurements have the same variability.
Runs test p	The runs test is a statistical test to decide whether the model curve deviates systematically from the data. It is based on the number of runs resulting from the fit. A run is a set of consecutive measurements which are above (positive residuals) or below (negative residuals) the measurement. Given the assumption that the residuals are randomly distributed, the probability p of the occurrence of a number of runs can be calculated. If p is small (eg. p<0.05) the measurements systematically deviate from the model curve. Such a finding signals that most likely an inadequate model was fitted and further investigations of the result are not sensible.
AUC	Area under the model curve.

4.9.1 Parameter Comparison across Regions (PKIN Parameters Explorer)

A convenient overview of the models and their parameters can be obtained using **View Par** in the **Tools** selection (lower right). It shows the same dialog window as the , except that the list entries correspond to the different regional TACs of the data set. The column maximum is highlighted in red, the minimum in green. Values can be sorted by clicking into the column headers, and the parameter order changed by dragging the column headers left/right. Data export is facilitated via **Copy to Clipboard**.

Note: The results shown on the **Regions** tab depend on the configuration settings. After changing the configuration, the window has to be closed and re-opened.

Configuration Settings

Include standard error in table	For each model parameter add a column with the % standard error. | vB	SE_vB	K1	SE_K1	k2	SE_k2	k3	SE_k3
0.05	NaN	0.067964	4.9342	0.125916	19.4044	0.026781	94.9827
0.05	NaN	0.067964	4.9342	0.125916	19.4044	0.026781	94.9827
0.05	NaN	0.069932	1.5686	0.13934	6.3284	0.037444	25.9652
0.045529	2.441	0.072562	1.5623	0.15751	6.0283	0.052887	19.5018
0.043419	2.3594	0.073413	1.3839	0.16245	5.3518	0.056237	16.5101
0.043474	3.5922	0.073424	2.5735	0.164586	10.1533	0.06053	29.352
0.043408	2.2296	0.073498	1.3719	0.164605	5.3149	0.05902	16.1573	
Include distribution statistics at table bottom	Show the lower section with min/average/median/max/stdv.
Use last region fits for table	Show the last successful fit from the history for each region. Otherwise the current regional model configuration will be listed, whether fitted or not.
Display tab with parameter plots	Visualization of the parameter values as a curve. Select the regions of interest on the **Parameters** panel. 	Regions	Fitting history	Parameter plots	Relative parameter plots	Model curves
No	Region	Model	Blood delay	vB	K1	k2	k3
1	Whole Brain	2 Tissue Comp...	0.0	0.05	0.067964	0.125916	0.026781
2	Cerebellum re	2 Tissue Comp...	0.0	0.05	0.080675	0.227288	0.018878
3	Cerebellum li	2 Tissue Comp...	0.0	0.05	0.079204	0.225141	0.018976
4	Striatum re	2 Tissue Comp...	0.0	0.05	0.075372	0.08494	0.003673
5	Striatum li	2 Tissue Comp...	0.0	0.05	0.082455	0.09473	0.009473
6	Caudatus re	2 Tissue Comp...	0.0	0.05	0.067731	0.081501	0.003047
7	Caudatus li	2 Tissue Comp...	0.0	0.05	0.075476	0.090835	0.008503
8	Putamen re	2 Tissue Comp...	0.0	0.05	0.085583	0.08794	0.003563
9	Putamen li	2 Tissue Comp...	0.0	0.05	0.087752	0.092447	0.0068
10	Frontal re	2 Tissue Comp...	0.0	0.05	0.077295	0.107137	0.015549
11	Frontal li	2 Tissue Comp...	0.0	0.05	0.078388	0.113582	0.020504
12	Temporal re	2 Tissue Comp...	0.0	0.05	0.077227	0.10984	0.027987
13	Temporal li	2 Tissue Comp...	0.0	0.05	0.078609	0.10918	0.024793	 The parameter plots are then shown on the **Display parameters** panel.

Display tab with relative parameter plots	Visualization of the normalized parameter values as a curve. Select the regions of interest on the **Parameters** panel. The **Display relative change curve** panel then shows the plot of each parameter normalized to the value of the last region.
Display tab with model curves	Visualization of multiple regional TACs together with their model curve. Select the regions of interest on the **Parameters** panel. The **Display model curve** panel then shows the data and the models.
Region filter	Specify a string (e.g. *right*) to filter the region list.
Model filter	Specify a string (e.g. *Compart*) to filter the model list.

4.9.2 Comparison of Model Curves for a Region

In addition to [comparing the same data in different PKIN windows](#) 78, model curves from different model fits can be plotted in a single curve display. The facility is accessible via the [fitting history](#) 59 mechanism, after enabling **Display model curve**.
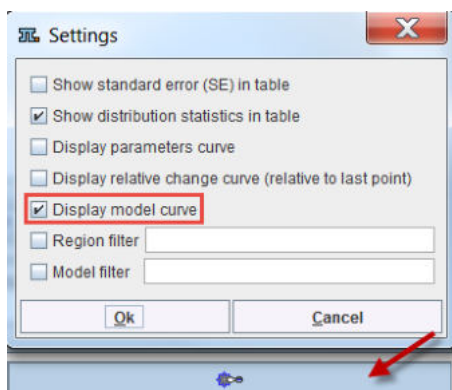
Now the model fits of interest can be selected on the **Parameters** tab,

No	Revision	Type	Date & Time	Region	Model	Blood delay	vB	K1	k2	k3	k4
1	6	Fit All	2016.10.06 13:58:24	Whole Brain	2 Tissue Compartments	0.0	0.05	0.067964	0.125916	0.026781	0.050104
2	7	Load	2016.10.06 13:58:46	Whole Brain	2 Tissue Compartments	0.0	0.05	0.067964	0.125916	0.026781	0.050104
3	8	Load	2016.10.11 08:59:51	Whole Brain	2 Tissue Compartments	0.0	0.05	0.067964	0.125916	0.026781	0.050104
4	9	Fit	2016.10.11 08:59:54	Whole Brain	2 Tissue Compartments	0.0	0.05	0.067964	0.125916	0.026781	0.050104
5	10	Fit	2016.10.11 08:59:59	Whole Brain	2 Tissue Compartments, K1/k2	0.0	0.05	0.067964	0.125917	0.026781	0.050104
6	11	Fit	2016.10.11 09:00:08	Whole Brain	1 Tissue Compartment	0.0	0.05	0.062301	0.084609		
7	12	Fit	2016.10.11 09:01:20	Whole Brain	2 Tissue Compartments, K1/k2	-4.51298	0.043367	0.073309	0.16307	0.057265	0.068774

and the corresponding model curves together with their targets inspected in the **Display model curve** panel.
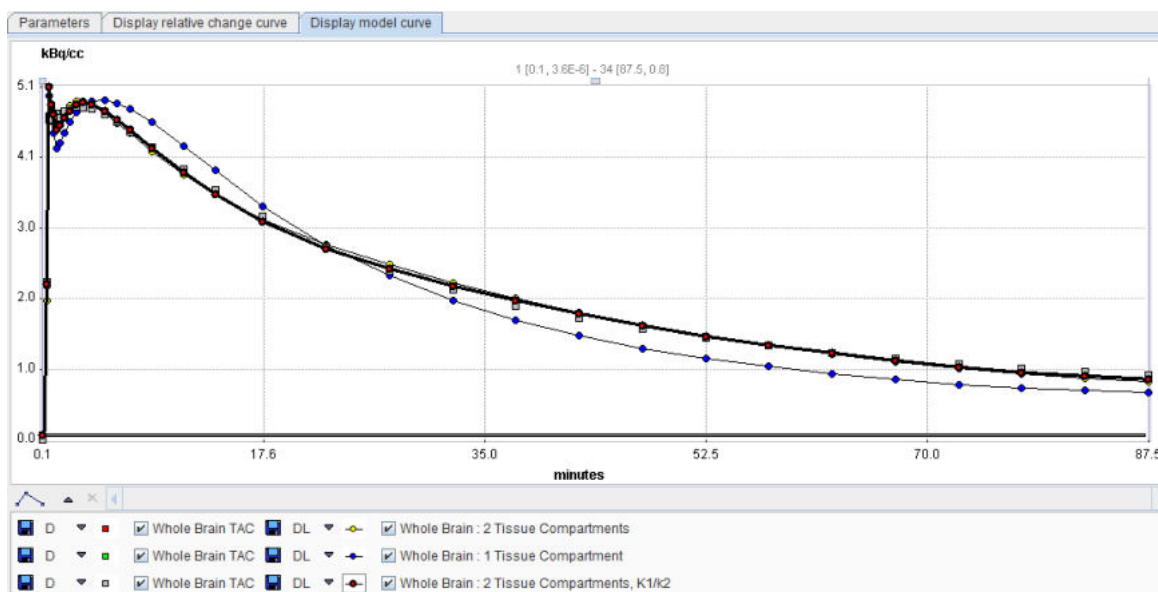
4.9.3 Comparison using two PKIN Windows

PKIN allows to examine different models and compare their numerical output using the History 59 mechanism. Sometimes it is also helpful to process the same data with different model configurations in parallel. This can be achieved using the **Study Compare Dialog** in the **Kinetic** menu.

A new dialog window is opened with a clone of the current data set. It supports all features of PKIN except for the functions related to data management. So the user can arrange the original PKIN window and the dialog window next to each other and process/visualize the same data in parallel.

4.9.4 Statistical Criteria for Comparing Models

The following criteria can be used for comparing different models which use the same weighting and are fitted to the same data. The notation is:

n: Number of independent measurements considered in the fit
p: Number of fitted parameters
w_i: Weight applied to residual of acquisition i

Akaike Information Criterion (AIC)

The Akaike Information Criterion [1] is defined by the formula

$$AIC = n \ln\left(\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2 / n \right) + 2p$$

If applicable, PKIN uses an adjusted procedure with a second order correction for small sample size (<40) [2]

$$AIC = n \ln\left(\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2 / n \right) + 2p + \frac{2p(p+1)}{n-p-1}$$

The more appropriate model is the one with the *smaller* AIC value.

Schwartz Criterion (SC)

The Schwartz Criterion is defined by the formula

$$SC = n \ln\left(\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2 / n \right) + p \ln(n)$$

The more appropriate model is the one with the *smaller* SC value.

Model Selection Criterion

Another modified version of the AIC criterion used in the *Scientist* Software (MicroMath, Saint Louis, Missouri USA) is the **Model Selection Criterion**

$$MSC = \ln\left(\frac{\sum_i w_i \left[y(t_i) - \bar{y}\right]^2}{\sum_i w_i \left[y(t_i) - \hat{y}(t_i)\right]^2} \right) - 2p/n$$

This criterion has the advantage that it is independent of the magnitude of the y_i. Opposed to the AIC and the SC the more appropriate model is that with the *larger* MSC.

F-Test

Two nested models can be compared by an F-test of their sum of squared residuals [3]. The idea is to compare the total sum of squares into a component removed by the simpler model and into a component additionally removed by the more complex model. For each component, the mean square (sum of squares per degree of freedom) is calculated. The residual mean square is an estimate of the variance of the original data. The ratio of the two mean squares is the F-statistic used to test for significance of the variance reduction by the additional parameters, as follows:

$$F = \frac{(Q_1 - Q_2)/(p_2 - p_1)}{Q_2/(n - p_2)}$$

where

Q_1 represent the weighted residual sum of squares or the simple model with p_1 parameters,
Q_2 the weighted residual sum of squares of the more complex model with p_2 parameters,
$p_1 < p_2$
The F-statistics has $(p_2-p_1, n-p_2)$ degrees of freedom. If the calculated F is larger than the tabulated

value at a specified p value, the reduction of the residual variation by the addition of the $(p_2 - p_1)$ extra parameters of the more complex model is statistically significant. Usually, significance p=0.05.

Note: in MS Excel the $F_p(p_2-p_1, n-p_2)$ can be calculated by the function FINV(p;p_2-p_1;n-p_2).

References

1. Akaike, H. A new look at the statistical model identification. IEEE Trans. Automat. Contr 1974, AC19: 716-723.

2. Motulsky H, Christopoulos A. Fitting Models to Biological Data using Linear and Nonlinear Regression. New York: Oxford University Press; 2004.

3. Carson RE, Parameter Estimation in PET, In: M. Phelps JM, and Schelbert H, eds. Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and the Heart., New York: Raven Press; 1986: 287-346.

4.9.5   Analysis of Parameter Sensitivity and Identifiability

The following two approaches can be employed to investigate whether a selected model is too complex for the data. The implementation in PKIN is based on the handout *Kinetic model evaluation with sensitivity functions and correlation matrices* by Dr. M.M. Graham, University of Washington at the Technical Exhibition of the Society of Nuclear Medicine Annual Meeting 1995 (JNM vol 36, no 5, P1208). As to our knowledge, there is no follow-up paper about this subject.

Sensitivity

If a parameter value is changed there should be some visual change in the model output. Some parameters will cause more change than other. The model is more sensitive to a parameter that causes more change in the output.

The sensitivity functions Sens(k_i) for the different parameters k_i are obtained by calculating the model function twice: with the initial parameter set, and after changing the parameter k_i by 1%. Then, the expression

Sens(k_i,t)= 100*[Model(k_i*(1.01), t)-Model(k_i, t)]/Model(k_i, t)

is calculated over time. When the 1% change of k_i has changed the output by 1% at a certain time the sensitivity function is equal to 1. In PKIN, the sensitivity functions are calculated for all model parameters, whenever the **Sensitivity** pane is selected. The example below shows the sensitivity functions of a FDG data set.
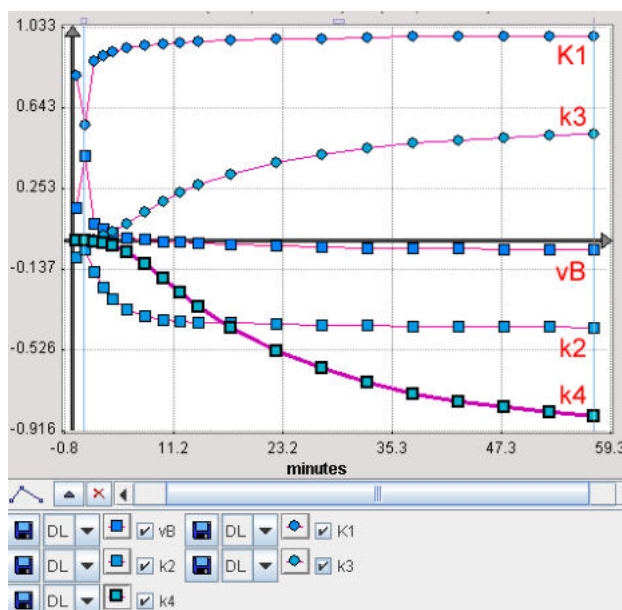
Examination of the sensitivity curves shows at what time a parameter has significant sensitivity and how sensitive a parameter is compared to another. If the sensitivity curves of two parameters have the same shape it is unlikely that one can tell which parameter has changed (ie. they are not identifiable).

In the FDG example above the model is quite insensitive to vB. Furthermore, the K_1 and k_2 curves have a quite similar (but opposite) shape throughout the acquisition duration, indicating that there is a substantial correlation between these parameters.

Identifiability

The model output must change in a unique way when changing a model parameter. If the change in the model output is the same when changing either of two parameters they can not be independently identified. In this situation the model must be simplified further, or one of the parameters can be fixed at a physiologic value. The latter approach is better since simplification usually means essentially setting one of the parameters equal to zero or infinity.

A more quantitative way to look at parameter identifiability is to generate a correlation matrix. It shows how the various parameters tend to correlate with each other. A low value, close to 0, means they do not correlate and that they are identifiable from one another. A high value, close to 1, means they are highly correlated and not independently identifiable.

The correlation matrix is calculated by:

1. generating the sensitivity matrix SM given from the sensitivity functions by SM(i,j) =Integral(Sens(ki,t)*Sens(kj,t));

2. inverting the sensitivity matrix SM(i,j), resulting in the covariance matrix;

3. normalizing the covariance matrix by dividing each element by the square root of the product of the corresponding diagonal elements; result is the correlation matrix .

The correlation matrix is shown in the **Sensitivity** pane. Using the **Save** button the correlation matrix and the sensitivity functions can be save into a text file.

Details	Increment	Restrictions	Sensitivity		
%Param. change	1.0				
Correlation matrix	vB	K1	k2	k3	k4
vB	1.0	-0.2457	-0.1473	-0.0104	0.3431
K1	-0.2457	1.0	0.8861	0.6102	0.2438
k2	-0.1473	0.8861	1.0	0.8864	0.5444
k3	-0.0104	0.6102	0.8864	1.0	0.8359
k4	0.3431	0.2438	0.5444	0.8359	1.0

Save

Note: Sensitivity functions are currently only supported for compartment models.

4.10 Special Processing Types

4.10.1 Parameter Sensitivity to Acquisition Duration

A standard task when analyzing kinetic data of a new tracer is assess the dependence of the parameters on the length of the available data. This type of analysis can easily be performed using the **Data shortening** option on the **Extras** panel. As soon as this option is enabled with a minimal data duration, the following happens when activating **Fit Current region**:
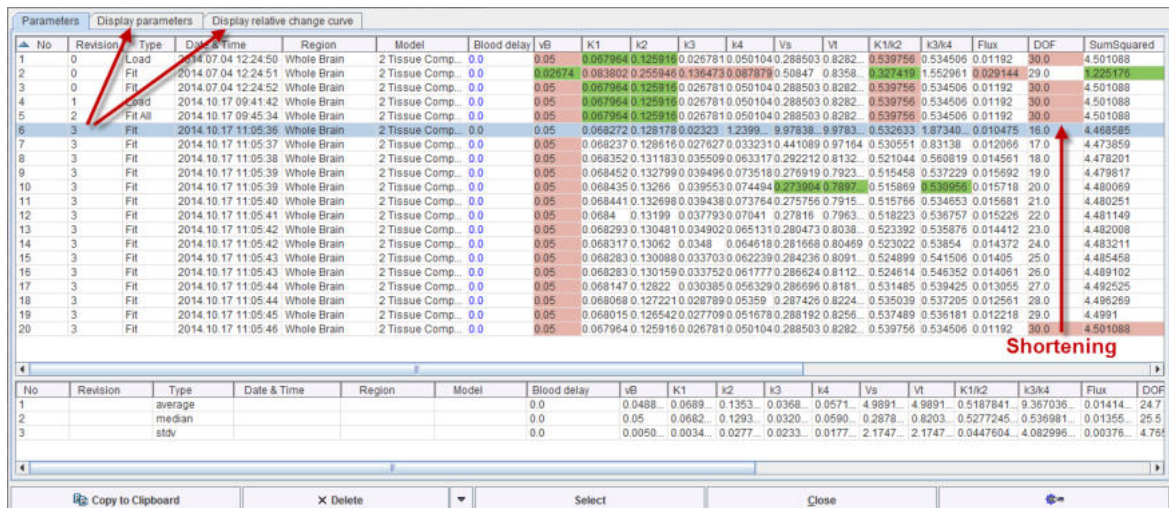
1. The set of initial parameters is created.

2. A fit is performed with the minimal data segment (e.g. the first 20 min), corresponding to a small number of Degrees Of Freedom (e.g. DOF=16). All other fit options on the **Extras** panel are also active are active.

3. An additional sample is added to the data segment and the fit repeated with the same initial parameters (DOF=17).
   This step is repeated until the full data segment has been fitted.

Results

The results are stored in the model fitting history and can be opened in the with the PKIN Parameters Explorer with the ▦ button. All fits of the sensitivity fits have the same **Revision** number. The data segment length is represented by the DOF column.

The results of the sensitivity analysis are most conveniently saved by selecting an entry with the appropriate **Revision** and using the **Save Selected Revision** function illustrated below. It saves the fitting results from all regions into a .kinPar file.
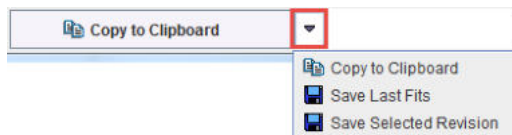
Sensitivity Visualization

The results can be exported via **Copy to Clipboard**, but the trend can also directly be visualized on the **Display parameters** and **Display relative change curve** panels. The selection in the list defines the data to be visualized:

- Selection of a single line as illustrated above: all entires with the same **Revision** number are used.

- Explicit selection of a subset of lines as illustrated below. In this particular example the Vt value degenerated for the shortest segment ($9.98*10^{94}$), which resulted in unusable plots. Therefore only the longer segment fits were selected.

When selecting the **Display parameters** panel the absolute parameter values are visualized. Each parameter corresponds to a curve and can be enabled/disabled with the checkboxes in the curve control area. The x-axis value corresponds to the number in the **No** column, so the length of the data segment increases to the right.
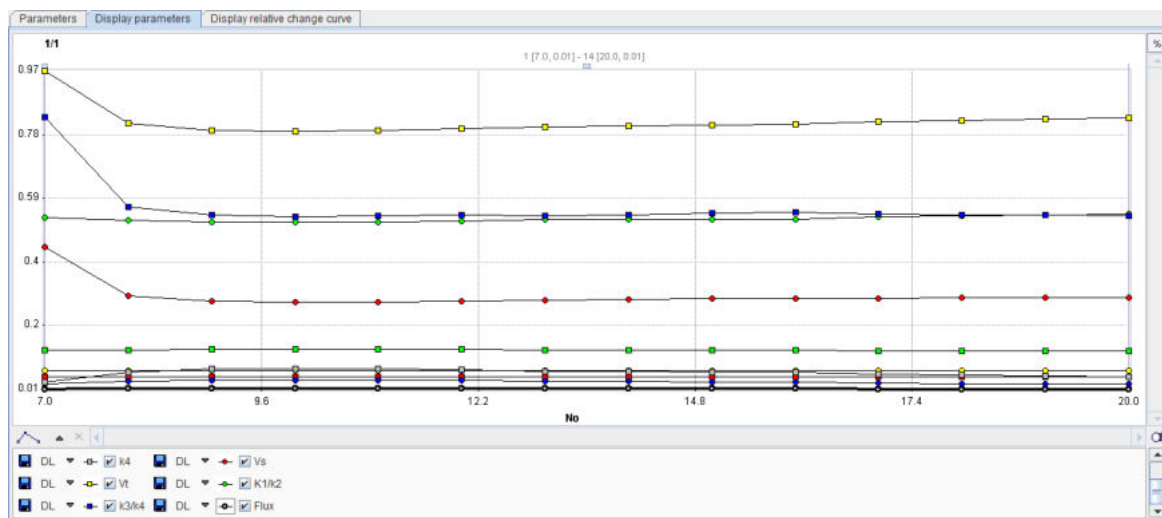
When selecting the **Display relative change curve** panel the same curves are shown, but the values are normalized to the last point (which in the case of the sensitivity fitting can be considered as the most reliable one).
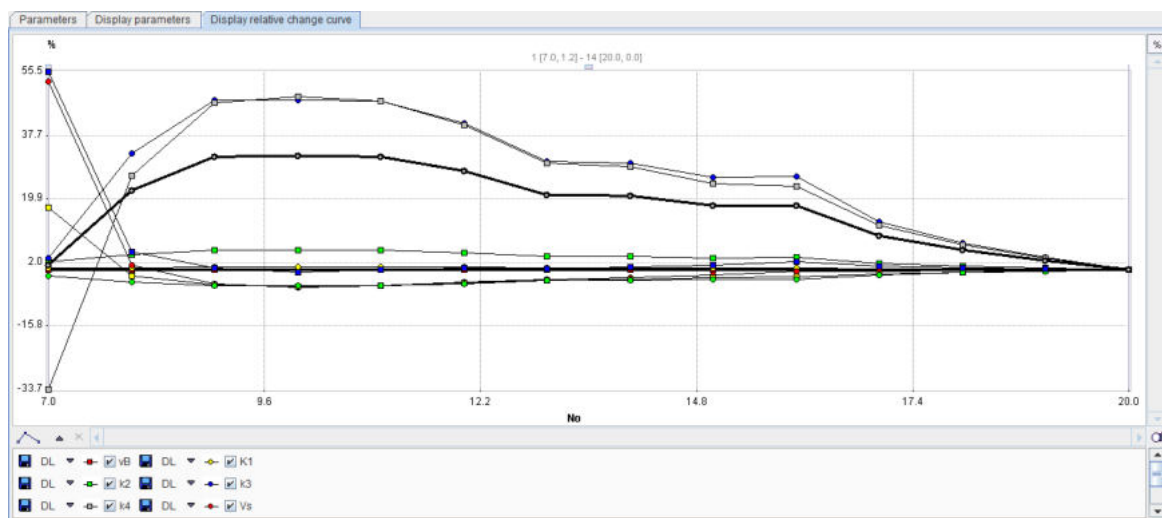
Leave-one-Out

The operation behaves differently, if a **negative interval time** is specified. In this case, not the whole end segment at the end is disabled, but only a single point, as indicated below. Using the model history, the user can easily step through the different fits with a single measurement disabled and see the impact on the result parameters.
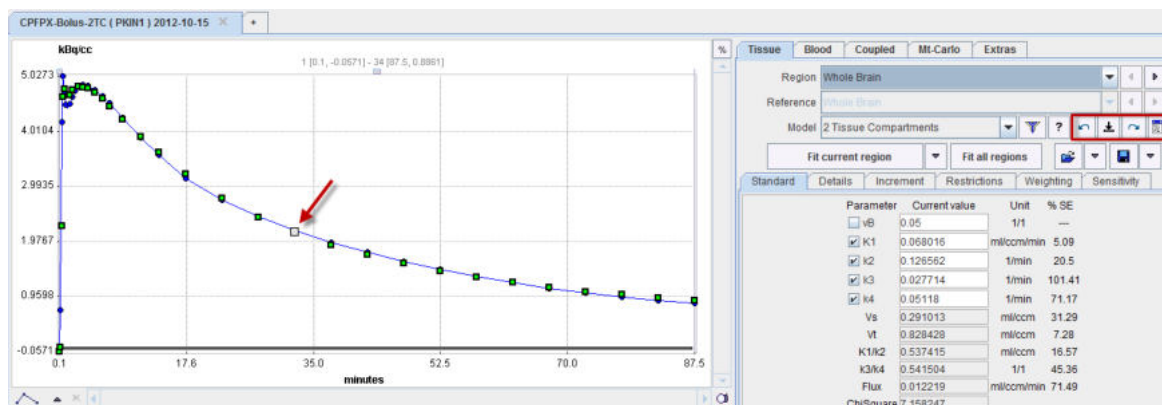
4.10.2 Monte Carlo Simulations

The purpose of performing Monte Carlo simulations in kinetic modeling is to get information about the standard error of the parameter values found in a fit. There are two different kinds of sources which contribute to the uncertainty of the parameters:

1. All the input data are measured and hence prone to measurement errors.

2. The model may contain more parameters than supported by the data, so that the effect of one parameter may be counter-balanced by another parameter.

The paradigm used for performing Monte Carlo simulations is described by Flannery et al. [11]. The basic idea is to simulate a series of measurements and statistically analyze the results when modeling these synthetic "measurements".

In PKIN Monte Carlo simulations can be performed for compartment models applied to a single tissue and models coupled across several tissues by selecting the respective option button on the **Mt-Carlo** panel.
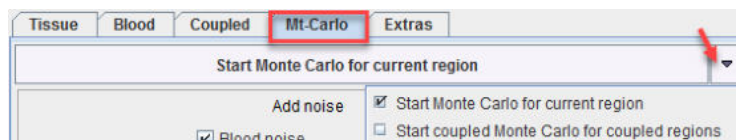
Single Tissue

Three types of "noise" can be defined. For each "noise" the distribution type as well as the variance has to be configured. After selecting the distribution a dialog window appears for defining the variance as described in the Residual weighting 56 for model fitting.

1. **Blood noise** to be added to the blood data for simulating noisy input curves. This option is only supported for blood models of type **Lin. Interpolation**.

2. **Model noise** to be added for simulating TAC noise. Note that here only the noise distribution needs to be selected. The noise variance is adopted from the **Weigthing** tab on the **Tissue** pane. If **Add noise to measured TAC** is not selected, noise is added to the tissue model curve, otherwise to the measured TAC. The latter e.g. allows studying the effects when fitting a simplified model to the data.

3. **Parameter noise** to be added to the starting parameters for disturbing the starting conditions from the ideal solution. For instance 20% noise can be added to the ideal parameter values.
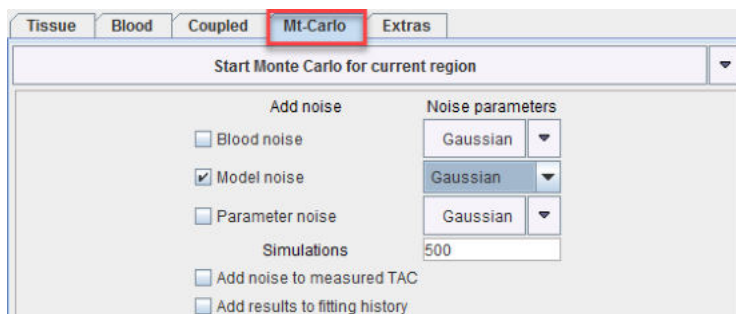
Three different distributions are available for noise generation, **Gaussian**, **Poisson**, and **Uniform**. They are applied for each individual measurement with the prescribed variance.

For the **Model noise** simulations there is also the **Bootstrap** method available. With the **Bootstrap** approach, the weighted residuals wr_i of the initial fit are used [73]. For simulating a noisy curve, these residuals are randomly selected and added to the model curve. Specifically, the noise for a frame j is constructed from a randomly selected wr_i of frame i by dividing it by the weight of frame j. As a consequence, it will have the same effect in the fit as it originally had in frame i.

When the **Start Monte Carlo for current region** button is selected the following processing starts:

1. An initial fit is performed. From then on it is assumed that the result parameters represent the "true" parameters, and the model curve represents the "true" measurement curve.

2. The number of **Simulations** times a noisy data set is prepared according to the definitions and then fitted. Noise is added to the model (or tissue) curve, and optionally the input curve. The "true" parameters, optionally disturbed by some noise, are used as starting values, and the fit to the noisy data performed. If **Add results to fitting history** is checked, the result is saved to the fitting history together with the noisy TAC. Otherwise, just the resulting parameter values are recorded.
Note: For non-compartment models the noise is added to the measured values, as the target may represent transformed data such as a graphical plot. For reference tissue models noise is only added to the target TAC.

3. After all runs have completed, the distribution of the result parameters is analyzed resulting in a mean and a standard deviation value for each fitted parameter. These values are shown on the **Standard** tab of the **Tissue** page, and the model curve calculated with the mean parameters is shown. Often, it does not follow the measurement as well as with the fitted parameters. The Monte Carlo results should now be saved, because as soon as a parameter is changed or a new fit is initiated, the results get overwritten.

It is possible to visualize a summary of the fit results during the Monte Carlo runs by switching back from the **Tissue** to the **Mt-Carlo** pane. In the curve display, a new curve **Monte Carlo** appears with vertical bars. The end points of these bars mark the minimal and the maximal value that any of the resulting model curves reached at a particular time point.
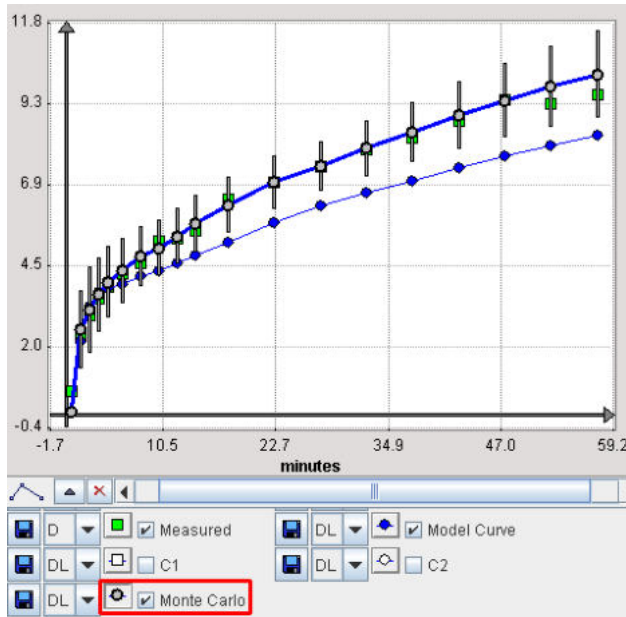
Fitting History

The value of using the fitting history 59 is illustrated below after a Monte Carlo simulation with enabled **Add results to fitting history**. Each entry from the simulation has a common **Revision** number. The **Monte Carlo Initial Fit** line contains the result of the first fit to the original data. If **Add noise to measured TAC** is not selected, the model curve is the curve to which the generated noise is added. The following entries **Monte Carlo Simulation** are the individual fits to the generated noisy TACs. The final line **Monte Carlo Result** represents distribution of all individual fits: the parameters are calculated as the average across the individual fits, and the standard error as their standard deviation.

Double-click into the history to show the noisy TAC and the fit result of a simulation. Use the arrows

to conveniently step through the simulations.

Note that the results of the simulations can also be visually presented by selecting all simulations in the **Parameters** history and selecting the other panels. The **Display parameters** and **Display relative change curve** show the individual parameters across the simulations as absolute and relative values, respectively. **Display mode curves** shows all noisy TACs with the respective fitted model curves.

The individual fit results can also be saved for dedicated statistics. To this end select an entry with the **Revision** of the Monte Carlo simulation, then use **Save Selected Revision** as illustrated below.
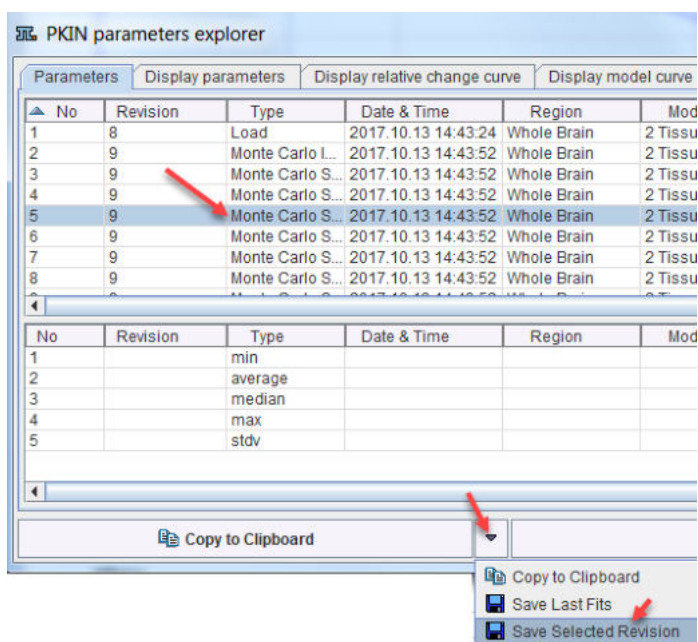
> **Note:** When saving a .km file, the history is included. Therefore the file created can become large when including extended Monte Carlo simulations.

Several Tissues Coupled

The same principle as for the single tissue Monte Carlo simulation applies to a coupled Monte Carlo simulation. It can be started by **Start Monte Carlo for current region** and uses the configuration prepared on the coupled 65 panel. **Model noise** uses the weighting individually defined for each coupled region. The fitting history of all coupled regions uses the same **Revision** number, so that all results can be exported at once.

4.10.3 Batch Mode

The **Batch Mode** serves for the sequential processing of multiple data sets. The processing, which can be applied to the data sets, depends on their format:

▪ KM file: A **.km** file saved from PKIN includes a complete definition of the blood interpolation model, the tissue model, weighting etc. for each region. Therefore, multiple processing types are supported including coupled fitting and Monte Carlo simulations. Additionally, during the fitting, the options 54 on the **Extras** pane such as parameter initialization and randomized fitting will be effective. **Note that the input file will be replaced by a new file with the results available in the fitting history** 59.

- Composite data file: A **.kmData** file contains only the data definition [36], except for the global specification of a model. Therefore, only the individual tissue model fitting is supported. The result will be saved as a new .km file with the same name as the input file, and with the results in the history.

Batch Facilities for .km Files

The **Batch Mode** entry from the **Kinetic** menu opens a dialog window for setting up the batch queue.
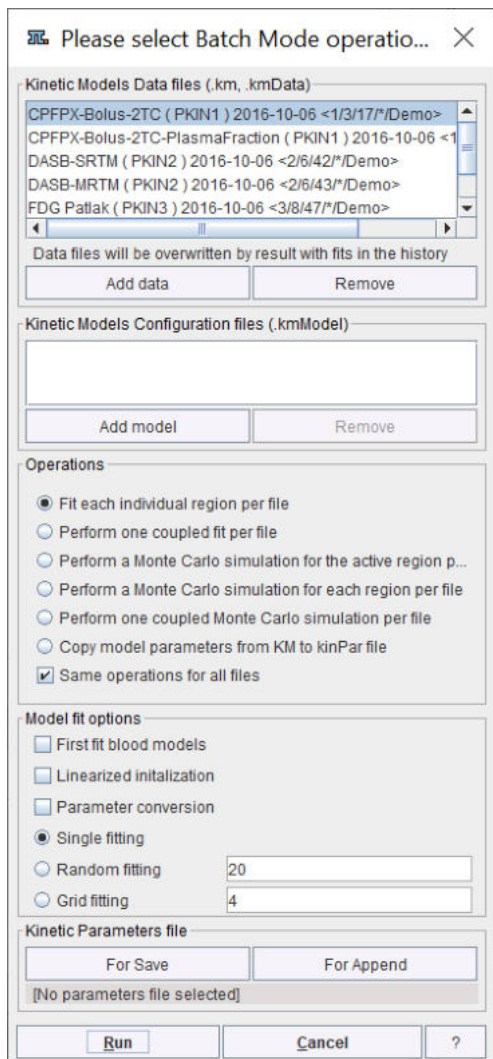
Use the **Add data** button for opening a data selection window and select the data sets to be processed from a database or the file system. Further data can incrementally be added, and selected list entries removed.

If only .km files have been selected it is assumed that appropriate configurations are included for the user's processing choice which is set by the radio button in the **Operations** section:

Fit each individual region	All regional TACs are fitted with the respective models as defined in the .km file.
Perform one coupled fit	Performs coupled fitting with the model and coupling as defined in the .km file.
Perform a Monte Carlo simulation for the active region	Using the noise and model definitions in the file a Monte Carlo simulation of the current TAC is performed.

Perform a Monte Carlo simulation for each region	As above, but applied to all regional TACs. Can be used to evaluate the sensitivity at different parameter combinations.
Perform one coupled Monte Carlo simulation	Monte Carlo simulation using coupled fitting as defined in the file.
Copy model parameters from KM to kinPar file	Just a convenience to summarize the parameters of a series of files into one tabular text file. Note that a result file must first be defined with the **For Save** button for the option to become available.

Fitting Options

The **Model fit options** give access to the mechanisms for improving objectivity and reliability of the results discussed in Fitting Options on Extras Panel 54 with one exception. The **First fit blood models** option is intended for cases, where interpolation functions are defined for the different blood components but not yet fitted. If

Batch with Model Configuration Files

The batch mode also allows fitting multiple models to each data file. To do so, corresponding model configuration files can be selected with the **Add model** button in the Kinetic .
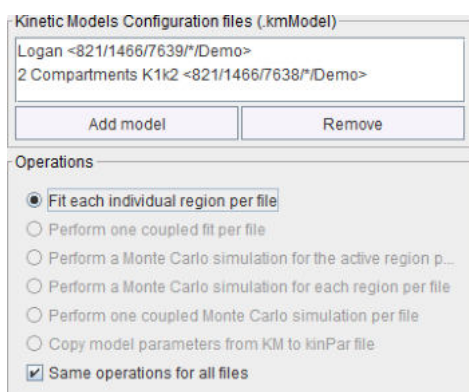
In this situation, only the **Fit each individual region** option is available. The results of the different model fits are saved in the regional model histories.

Batch Results

The **For Save** and the **For Append** buttons can be used to specify a file as a container for saving the result parameters of the batch run. These results are in the **.kinPar** and can be transferred to the R console for performing statistics.

For allowing visual inspection of the results each original data file is replaced by new file. It contains in the history 59 all model fits from the batch, so that a user can simply load the file and step through the fits using the history buttons.

Starting the Batch

The **Run** button starts processing, and PMOD will be blocked until processing completes.

4.10.4 Fitting Blood Shape Parameters and Tissue Parameters together

The PKIN tool allows the simultaneous fitting of the shape parameters of the blood models and the kinetic parameters of the tissue model. This fitting mode can be activated by checking the **Fit blood** box on the **Extras** pane. It is active in the fitting of the single tissue TAC as well as in coupled fitting.

With **Fit blood** on, ALL parameters of the **Whole blood** and the **Plasma** model (but not the plasma fraction or parent fraction parameters) which have the fit check on will be modified during the fit of the kinetic tissue model. Note that the blood models are not fitted to the actual blood measurements in this process, but it is only the impact of the blood curve on the calculated tissue model curves which results in the modification of the blood model parameters.

4.10.5 Dispersion Correction of Automated Blood Samples

Blood Sampling Setup

Automated blood sampling is the preferred method for measuring the activity concentration in whole blood. In such a setup, a catheter is inserted into an artery, and blood continuously run through a detector, which measures the radioactivity from the time of tracer injection until the end of the PET acquisition. If needed, automated blood sampling can be stopped when the blood concentration changes have become slow, and some manual blood samples be withdrawn at later times.

A typical blood sampling setup is illustrated below with a catheter in the radial artery, which is run through a coincidence detector (twilite, **www.swisstrace.com**) and a pump which ensures constant blood drawing speed. Three-way valves serve for occasionally taking blood, which is needed for the metabolite analysis.

Blood Dispersion

Because the blood needs to travel an extra distance outside the body until it reaches the detector, the blood measurement is delayed. Furthermore, the time course of the concentration is altered, because fast concentration changes are smoothed in the catheter, an effect called "dispersion". In

kinetic modeling, results can be biased if dispersed blood information is used, particularly for short measurements such as ^{15}O-water bolus studies for quantifying tissue perfusion.

4.10.5.1 Dispersion Correction Methodology

Dispersion Correction

Several dispersion correction methods have been developed. Most of them describe dispersion as a convolution of the true concentration curve with a dispersion function, and correction amounts to a numerical deconvolution which produces results suffering from excessive noise. Munk et al. [1] have developed an alternative approach which circumvents numerical deconvolution. It describes transport of blood through a catheter by a "transmission-dispersion" model which includes two components: molecules which travel undisturbed in the inner of the catheter (convective flow), and molecules close to the catheter wall to which sticking occurs (stagnant flow).

The true (corrected) blood activity concentration $C_B(t)$ can be calculated from the measured concentration $C_{mB}(t)$ as follows.

$$C_B(t) = \frac{C_{mB}(t+T)}{1-\alpha} - \frac{\alpha k}{(1-\alpha)^2} \int_0^t C_{mB}(\tau+T)e^{-k(t-\tau)/(1-\alpha)}d\tau$$

There are three parameters in the equation which are characteristic for the experimental acquisition setup:

- the transit time T,

- a parameter k[1/min] which refers to the stickiness of the catheter for a tracer, and

- the stagnant fraction α. If $\alpha=0$, no dispersion occurs, just a delay. $\alpha=1$ is not allowed in the equation, so $0 \leq \alpha < 1$.

The effect of α and k on the corrected curve shape is illustrated below with two plots from [1]. The dashed line represents the dispersed, measured concentration, and the solid lines the true concentration recovered by correction.
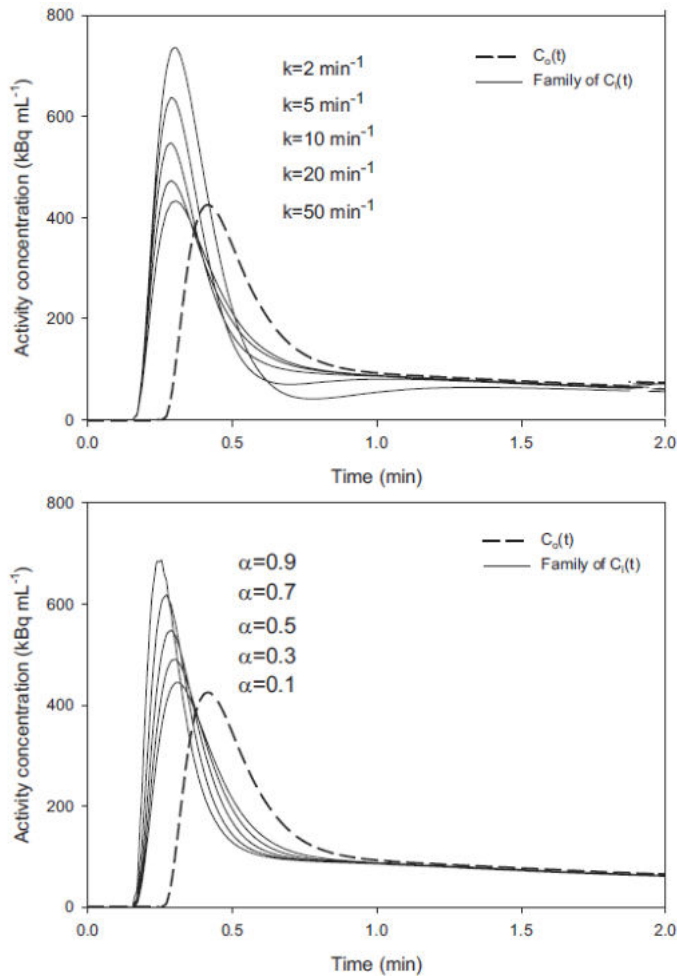
Calibration Measurement

The parameters k and α have to be obtained from a calibration measurement with exactly the same conditions as the live experiment, i.e. with same catheter length, withdrawal speed and tracer as described in [1]. Basically, two beakers are prepared: one beaker with blood only, the other with blood and tracer (taken 1min after tracer infusion). A three-way tap is used with one catheter leading to the blood sampling system, and the other two into the beakers. Blood sampling is started with connection of the blood-only line to the detector for measuring the baseline with no radioactivity. Then the tap is switched to the catheter with blood and tracer. Correspondingly, the measured radioactivity is rising up to a constant hight. Sometime later the tap is switched back to the blood-only line, and the radioactivity is decreasing back to the baseline. Instead of the true rectangular shape of the concentration at the tap a concentration shape similar to the dispersed rectangle below [1] is measured.
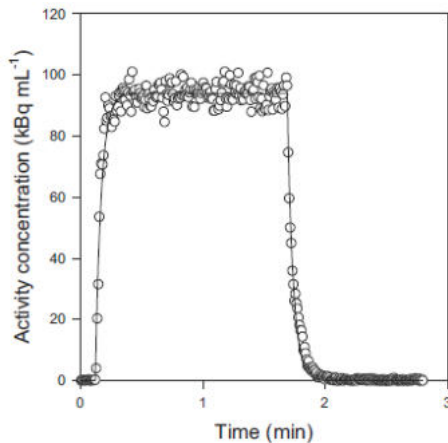
Formula can be derived [1] describing the step-up as well as the step-down edge as a function of the dispersion parameters k and α, as well as the transit time T:

Step-up:

$$C_u(t) = \begin{cases} 0 & t < T \\ C - \alpha C e^{-k(t-T)} & t \geq T \end{cases}$$

Step-down:

$$C_d(t) = \begin{cases} 0 & t < T \\ \alpha C e^{-k(t-T)} & t \geq T \end{cases}$$

By fitting these functions to the measurement, the parameters can be determined and subsequently used in the correction of any live measurement using the same setup.

Reference

1. Munk OL, Keiding S, Bass L: A method to estimate dispersion in sampling catheters and to calculate dispersion-free blood time-activity curves. Med Phys 2008, 35(8):3471-3481. **DOI**

4.10.5.2 Dispersion Calibration in PKIN

Calibration Measurement

A calibration measurement should be performed as **described** 91, measuring the response in the blood counter to a rectangular input activity. Note that the measured data have to be decay corrected and calibrated to kBq/cc.

Fitting of the Dispersion Parameters

In PKIN, please start a new workspace and load the measurement with the menu item **Load Whole Blood Activity**. On the Blood tab, switch the **Whole Blood** model to **Calibration: Step-up** as illustrated below.
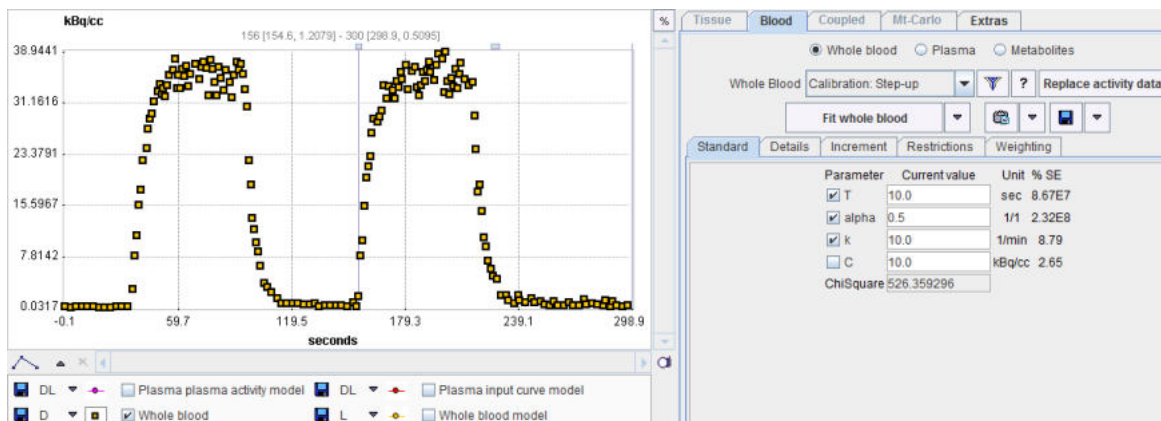
Mask all samples except for a baseline, rising edge and the following plateau as follows:

1. Right click into the curve area. In the context menu
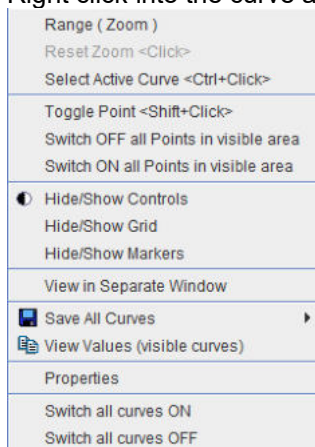
    select **Switch OFF all Points in visible area**. Consequently all samples appear gray, meaning they are not considered in fitting operations.

2. Open the context menu again and select **Range**. Enter the start/end times of the relevant section and close with **Ok**.
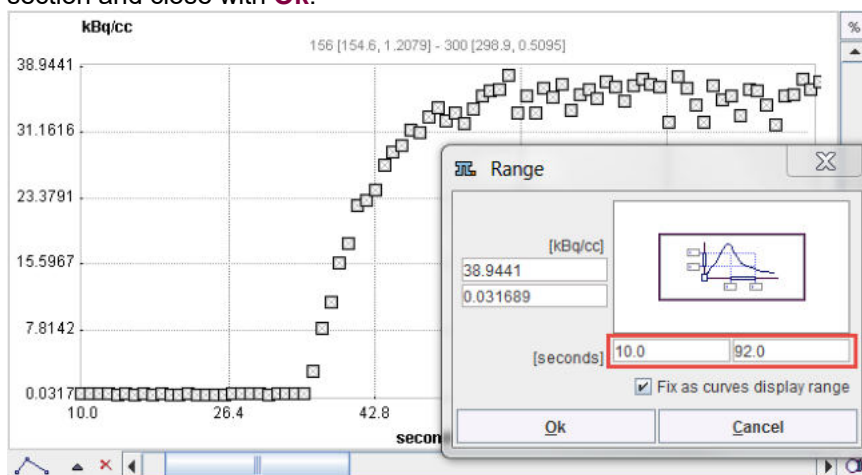
3. Open the context menu again and select **Switch ON all Points in visible area**.

Next comes the fitting of the step-up model. Enter the time where the signal rises as a starting value for the **T** parameter, the known concentration value as the **C** parameter, and enable the fitting flags as illustrated below.
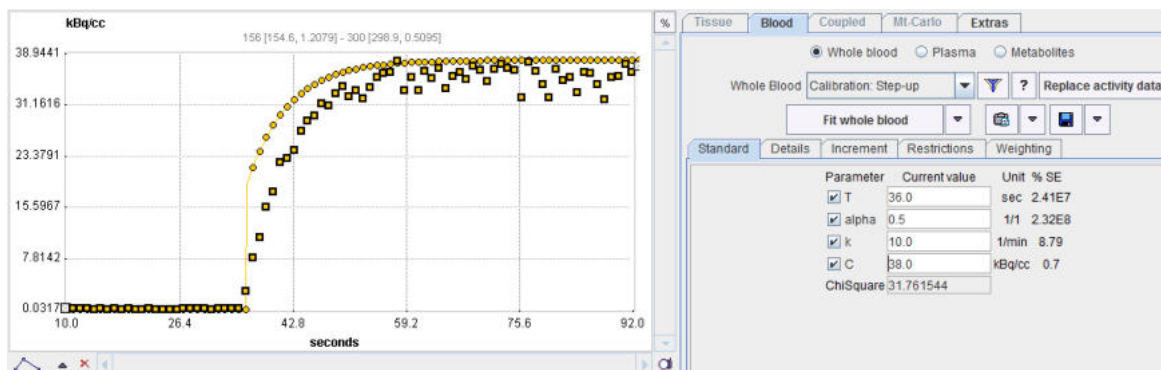
With **Fit Whole Blood** the model curve can be fitted to the section.
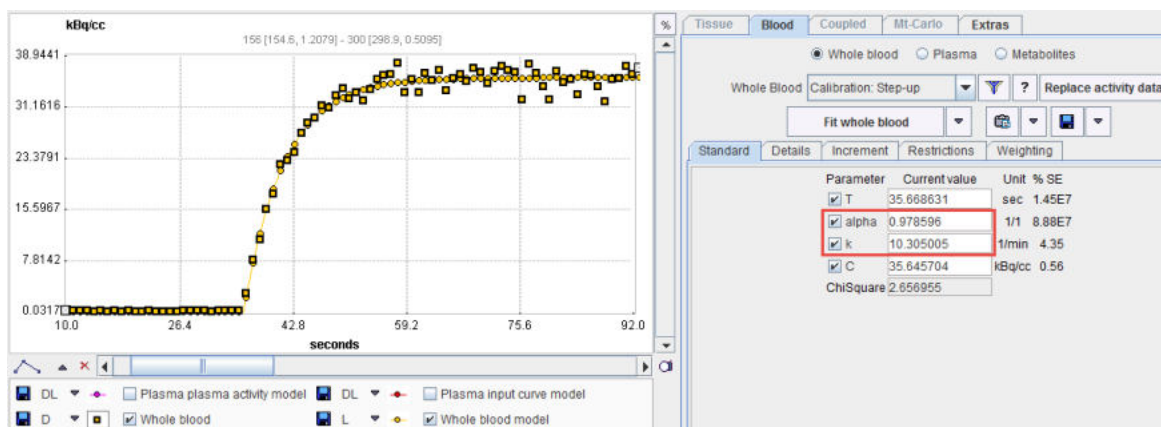
A similar fitting can be done with the decreasing edge and the model **Correction: Step-down**. Fitting the different parts of the calibration experiment provides several sets of the dispersion parameters, which allows determining their average values. Those values of the **alpha** and **k** parameters can be applied for the correction of the actual blood curve of live experiments.

Recommendations by Methodology Author Ole Munk

alpha has an impact on the noise in the dispersion-corrected input functions. If **alpha** is allowed to get close to 1, then the noise increases (too) much (Fig.8 in Munk et al.). Therefore, in practice, **alpha** can be fixed at a reasonable value, eg. 0.75, and only **k** fitted along with the two "known" parameters **T** and **C**.

Notes:

1. The parameters can be tracer-dependent. It takes less than an hour to do the calibration measurement and the parameters can be re-used for all future measurements using the same blood sampling setup.

2. Dispersion correction is only important when modeling fast processes such as blood flow. When estimating binding potentials and other "slow processes'", dispersion correction is considered less important.

4.10.5.3 Dispersion Correction in PKIN

Correction of Whole-Blood Curve

In PKIN, please start a new workspace and load the measurement with the menu item **Load Whole Blood Activity**. On the **Blood** tab, switch the **Whole Blood** model to **Calibration: Correction** as illustrated below.
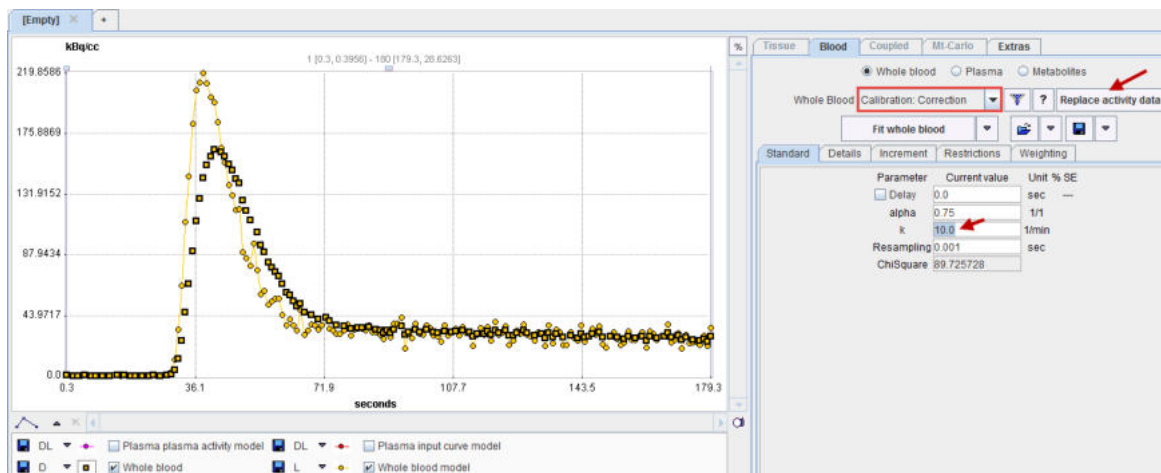
Next, enter the values for **alpha** and **k** determined with the calibration experiment. The dispersion corrected blood activity is shown as the **Whole blood model** curve. The **Delay** parameter represents the delay of the corrected curve relative to the blood arrival at the target tissue, as usual.

From now on, the corrected whole blood activity will be used in calculations such as spillover correction, or calculation of the plasma activity using a plasma fraction function.

Fitting of Smooth Function to Corrected Curve

In case the correction introduced substantial noise, a smooth function may be fitted by applying one of the usual whole blood models as follows:

1. **Replace activity data**: Use this button to replace the original (uncorrected) data by the corrected curve.

2. Select an appropriate Whole Blood model, in the example below **Gamma + 2 Exponentials**.

3. Use **Fit whole blood** to adjust the model to the dispersion corrected whole blood curve.
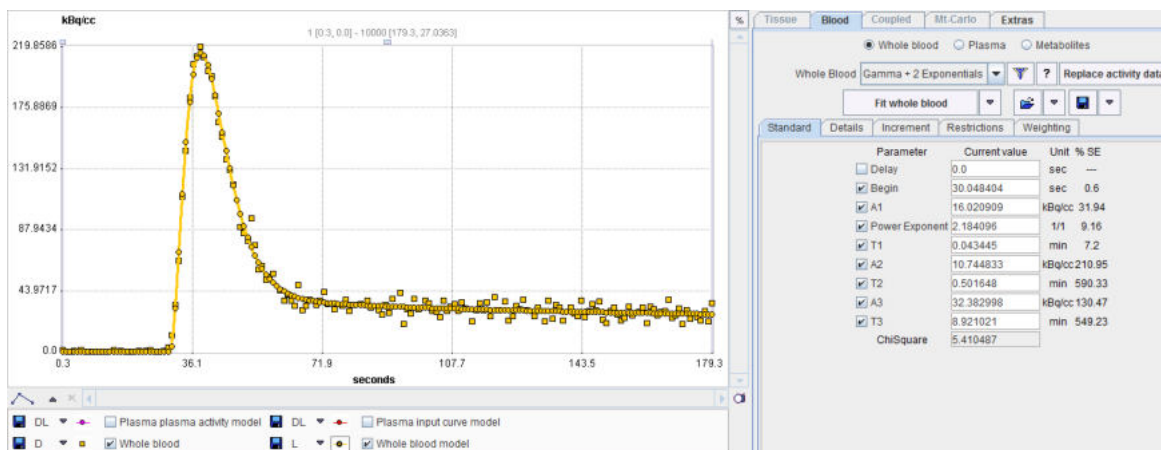
4.11   Convenience Tools

In the lower right part of PKIN there is an ensemble of user interface elements supporting some auxiliary tasks.

4.11.1 Changing Display Types

The **Display type** selection allows choosing which information is shown in the main curve area.
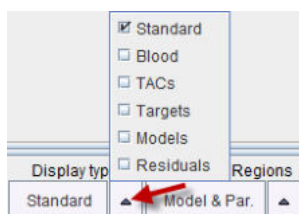
Standard shows all curves related to the current region. **Blood** shows only the blood activity, **TACs** only the measured tissue data, **Targets** all regional target curves to be fitted,
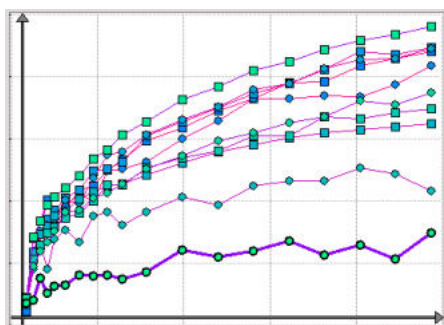
Models all fitted model curves,
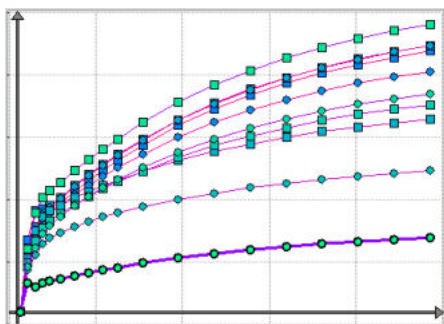
and **Residuals** all of the regional residuals.

4.11.2 Copy Operations

Copy to all Regions	This multi-function button can be used to propagate a model from the current region to all regions in the study. **Model & Par.** copies the model with the parameters (which can then be used as starting values for **Fit all regions**). **Model** copies the model structure, with the current parameters. **Weighting** copies the current definition how the residuals are weighted. **Valid** copies the definition of the currently valid points to all regional TACs.
Copy Blood Curves	This multi-function button allows transferring activity curves between the tissue and the blood. **Region to Plasma** copies the current TAC to the input curve. **Region to Whole Blood** copies the current TAC to the whole blood curve.

	Plasma to Whole Blood copies the input curve to the whole blood curve. **Whole Blood to Plasma** copies the whole blood curve to the input curve.

4.11.3 Auxiliary Tools

The **Tools** multi-function button is particularly helpful, if the PKIN tool is opened as an intermediate dialog and hence has no menu available. In this case, **Save KM**, **Save Par**, **Append Par** just allow to save the data as a .km file, as a parameter summary text file, and to append to a latter file.

```
☑ View Par.
☐ Save Par.
☐ Append Par.
☐ Save KM File
☐ Edit Data
☐ Edit Patient
☐ Add Comment
```
```
Tools
View Par.   ▲
```
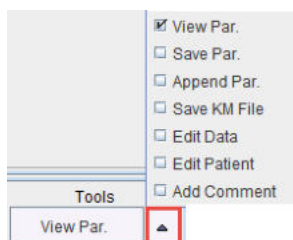
View Par opens a dialog window and shows a quick summary of all regional model parameters as well as the statistical criteria, see above| 75|.

Edit Data allows editing/processing the data values and generating new TACs, for instance by averaging TACs or adding noise, see below| 102|.

Edit Patient allows changing the demographic patient data as well as the radionuclide, see below| 103|.

Comments opens a dialog window for entering arbitrary comments, see below| 104|.

4.11.4 Parameters Aggregation

The **Kinetic** menu contains an entry **Parameters Aggregation**. Its purpose is to concentrate the parameter values which have been saved in **KM Parameters Files** (***.kinPar**) for statistical analysis. The general concept and the details of data aggregation are explained in the *PMOD Base Functionality Guide*.

Component Selection

Parameters Aggregation opens a dialog window with two tabs as illustrated below.The **Select** pane allows defining the files from which the parameters are extracted.
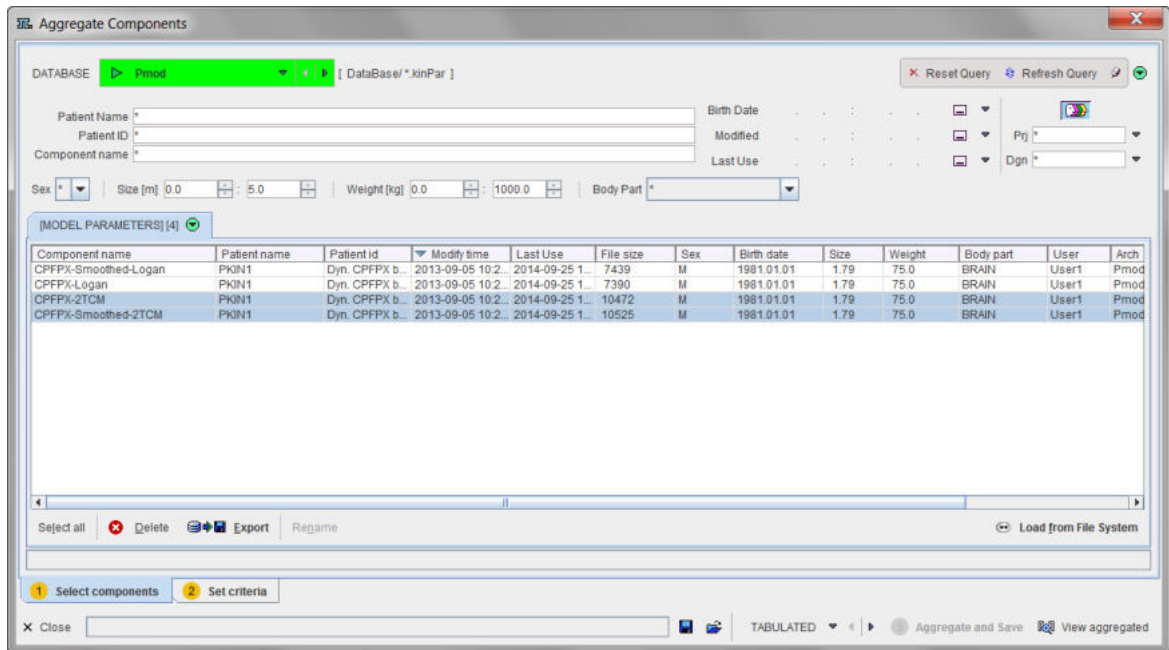
They may be available in a database as in the example above, or in a disk directory. In the latter case use **Load from File System** to define the directory were the files reside. All appropriate **.kinPar** data sets are listed. Select all data sets to be used for the aggregation and then switch to the **Set Criteria** pane.

Content Selection

The upper part **Reorder Selected Components** lists the data sets which have been selected for aggregation. They can be reordered if needed.
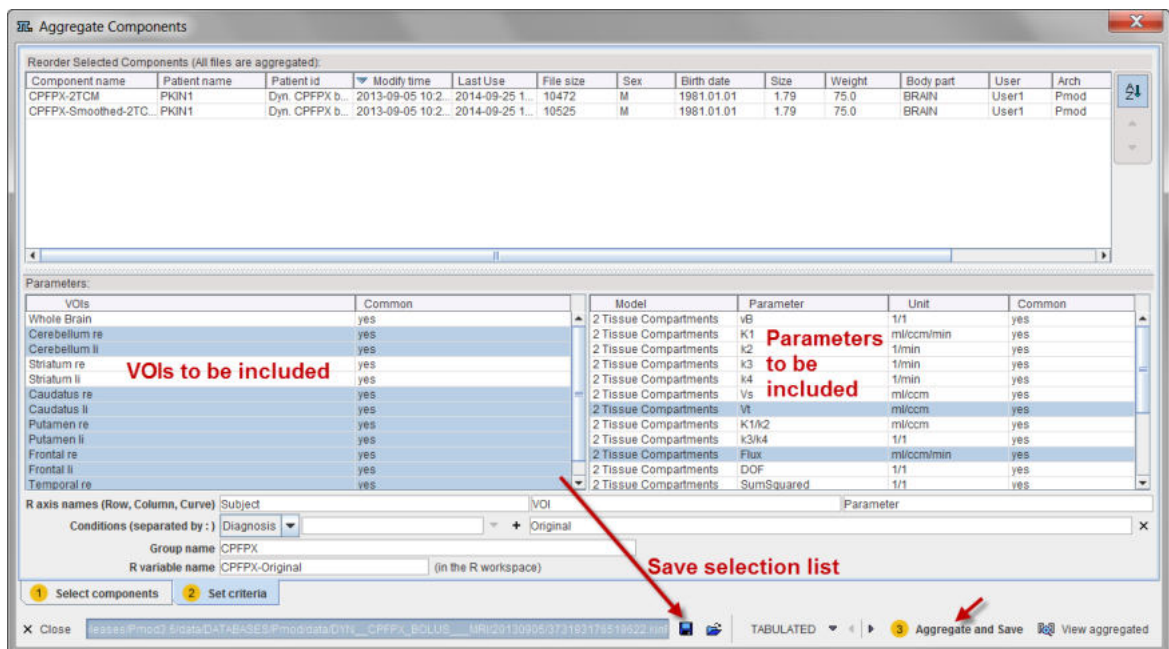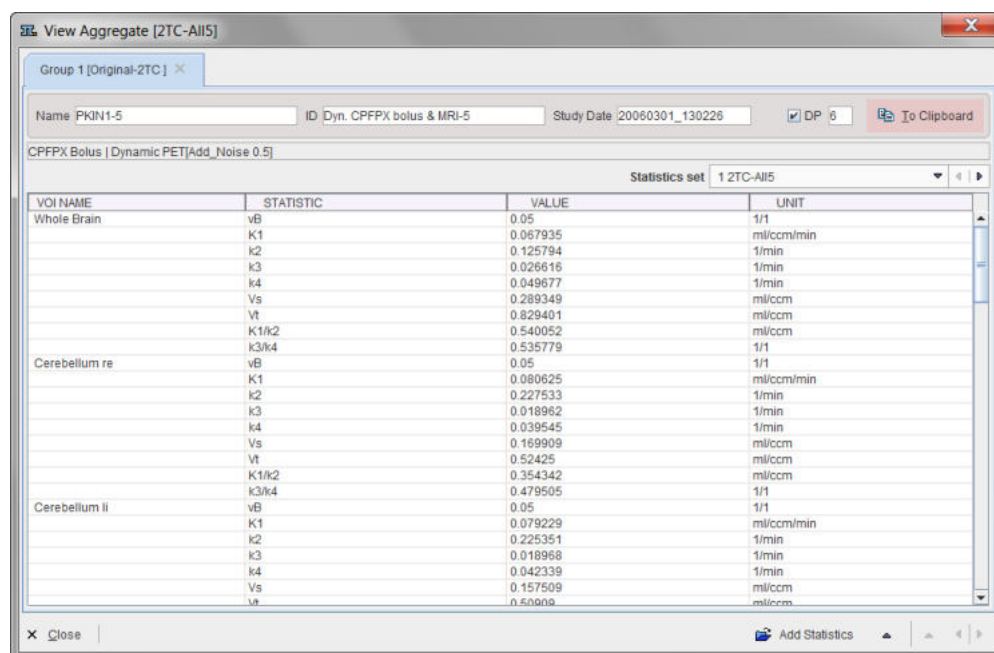
The **Parameters** section shows the available information. The left part lists the available VOIs, the right part the kinetic model parameters. A **yes** label in the **Common** columns indicates that all of the kinPar files include the particular element. Otherwise, a **no** label is shown. Note that entries which are not available in a data set will result in a **NaN** value in the aggregate.

Data Aggregation

Select the VOIs and parameters to be included so that they are highlighted, and activate **Aggregate and Save.** Specify the name of a database table, or a file name if the database is not used. When opening the saved aggregate with the **View aggregated** button, the statistics window appears with a selection for the **Statistics set**.

Aggregated parameters can also be opened again using the **View Aggregated** button from the taskbar to the right.
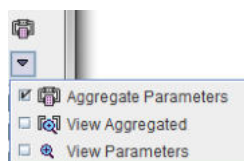
Application Cases

A typical example is the aggregation of the results of a test study in a test aggregate, and the results of the same population in a retest study in a retest aggregate. The two aggregates can then directly be used for a test-retest analysis using the PMOD R console.

Another example is the comparison of two analysis methods. In this case the results of the different methods would be aggregated in corresponding aggregates, which can then be compared with a Bland-Altman analysis.

4.12 Editing Facilities

4.12.1 Disable Measurements for Removing Outliers or Shortening the Fitted Data Segment

Occasionally there might be the need to disregard sample points when evaluating the matching criterion, for example to exclude an outlier, or to study the stability of model estimates with successive shortening of the acquisition duration.

In PKIN this can be easily achieved by (temporarily) disabling samples. First select the **Measured** curve by selecting it in the controls area or by **CTRL+Click** at a point. The green measurement points must appear highlighted in the display. Then individual points can be disabled by **SHIFT+Click** on them. For entire ranges it is advised to zoom into the region (drag left mouse button), then activate the context menu (right mouse button) and **Switch OFF all Points in visible**

area. This operation is illustrated below
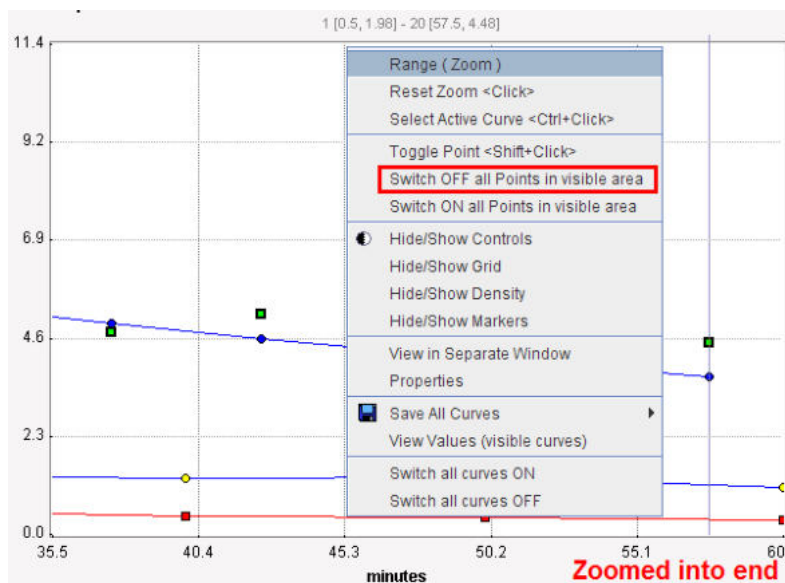
resulting in a "shortened" acquisition for fitting purposes:
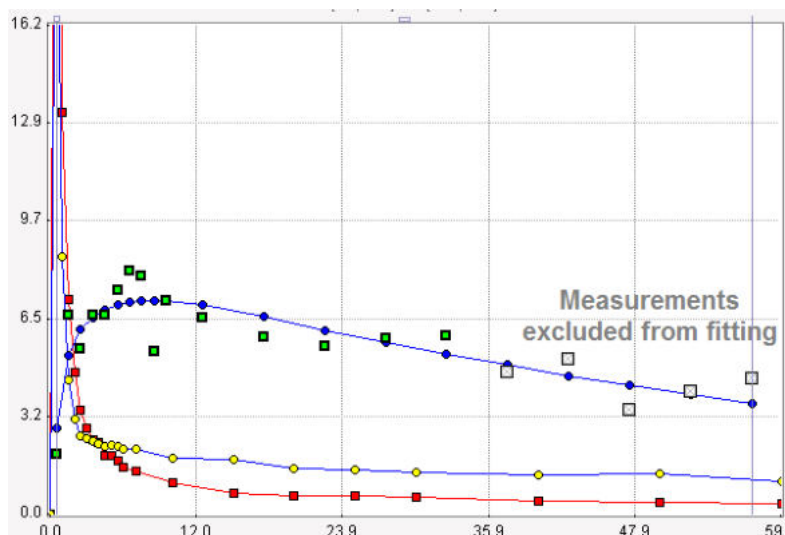
Disabled measurements appear in grey. They can again be enabled by a second **SHIFT+Click,** or by **Switch ON all Points in visible area** in the context menu.

Testing the Impact of Study Duration on Parameter Estimates

A frequent task is to find out the minimal study duration which allows the reliable estimation of a parameter. Such an analysis can be performed in PKIN as follows:

1. Ensure that the appropriate model has been configured for all regional TACs and **Fit all Regions**. Save the result parameters to a file using **Kinetic/Save KM Parameters File/Save**.

2. Disable the last valid measurement for a regional TAC.

3. Propagate this definition of valid points to all regional TACs using **Copy to All Regions/Valid** as illustrated below:
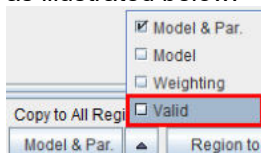
4. Fit again the model in all regions using the **Fit all Regions** button.

5. Add the parameter results from the shortened acquisition to the previous results using **Kinetic/Save KM Parameters File/Append**.

Repeat steps 2-5 continually shortening the acquisition until the parameter estimates degenerate. Then all data is available in a single file which can be opened in a program such as MS Excel for a statistical analysis.

4.12.2 Edit Data and Create New Curves

The **Edit Data** button in the **Tools** list brings up a dialog window which allows to examine and manipulate the TAC data of the current data set.
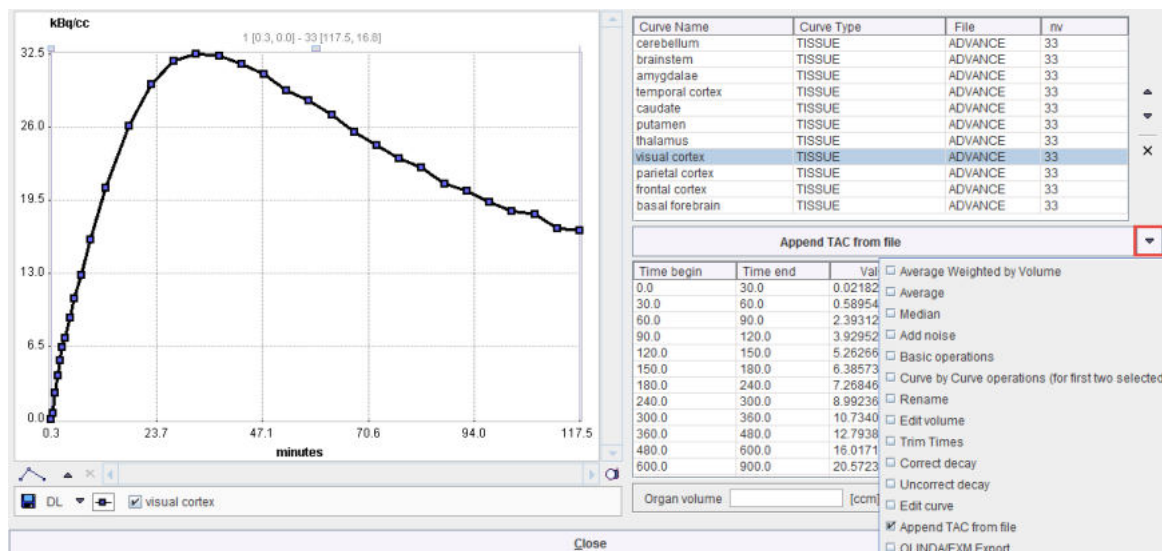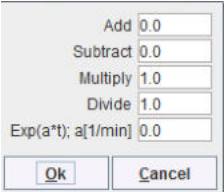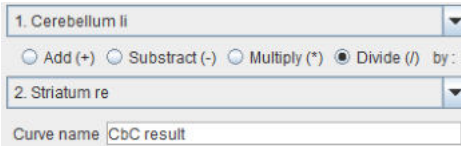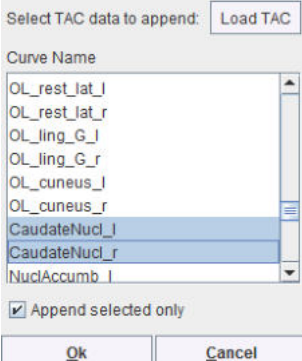
The upper section lists the different curves. The blood-related curves are at the top, then come the regional TACs. The arrows to the right can be used to change the TAC ordering, and a TAC can be removed by the **x** button.

The lower section lists the data of the selected curve. Shown for each sample are the acquisition start and end times, the measurement value (usually the VOI average), its standard deviation (the VOI stdv, if available), and the VOI volume. Note that the volume may vary if the VOI definition changes throughout the time course. The values of the tissue TACs can be interactively edited by clicking into a cell and changing the number.

The configuration button between the lists houses the following operations to modify TACs and generate new TACs which will be appended to the list.

Average Weighted by Volume	When several curves are selected, this button allows calculating the volume-weighted average TAC.
Average	TAC averaging with equal weights.
Add noise	Creates a copy of the selected TACs and adds noise according to the definition defined in a dialog window.
Basic operations	Applies simple arithmetic operations to the values of the currently selected curves, and allows multiplying a curve by the values of an exponential function.

	Add 0.0 Subtract 0.0 Multiply 1.0 Divide 1.0 Exp(a*t); a[1/min] 0.0 Ok Cancel
Curve by Curve operations	Arithmetic operations between the values of two selected TACs. 1. Cerebellum li ○ Add (+) ○ Substract (-) ○ Multiply (*) ● Divide (/) by : 2. Striatum re Curve name CbC result
Rename	For renaming of the currently selected curve.
Edit volume	Change the volume of the selected TAC.
Trim times	Check for frame time overlaps of the selected TACs and correct.
Correct decay	Apply a decay correction to the selected TACs using the isotope of the study [103].
Uncorrect decay	Undo the effect of decay correction for the selected TACs using the isotope of the study [103].
Edit curve	Edit the data of the selected curve in a text editor as described below.
Append TAC from file	Opens a facility for appending regional TACs stored in a file. After selecting the file with **Load TAC**, the regions are listed so that the user may select a subset. With **Ok**, the regional curves are appended to the existing ones. Select TAC data to append: Load TAC Curve Name OL_rest_lat_l OL_rest_lat_r OL_ling_G_l OL_ling_G_r OL_cuneus_l OL_cuneus_r CaudateNucl_l CaudateNucl_r NuclAccumb_l ☑ Append selected only Ok Cancel
OLINDA/EXM Export	This entry is applicable only for the OLINDA Residence Times [182] dosimetry model. It creates an input file to the OLINDA/EXM program.

4.12.3 Edit Patient and Change Isotope

The **Edit Patient** button in the **Tools** list brings up a dialog window which allows you to examine and change the demographic information of the current data set.

In case the TAC data was transferred from PVIEW to PKIN, this information is automatically filled in from the image data (if available in the data format). However, the contents can also be edited and saved if required. If the patient is already in the database, the **IMPORT PATIENT INFO FROM** facility can be used. With the **DATABASE** button a selection window opens which allows choosing an image series from the database. The required information will be retrieved and filled into the text fields.

Note the **SUV PARAMETERS** tab which gives access to the isotope definition.

This information is relevant for some models as well as calculated residual weighting 56.

4.12.4 Comments

The **Add Comment** button in the **Tools** list allows incrementally adding descriptive text to the data set being processed. It opens a dialog window with two areas: a list of comment entries with date and name of the creator in the upper part, and the actual text of the selected comment entry in the lower part.

To create a new comment entry select **Add**, type the comment into the lower text window, and complete editing by **Set**. This operation creates a new list entry which can be selected to show its contents, changed with the **Edit** button, or removed with **Delete**.

Note that you have to use **Save KM File** to include updated comments permanently into the data set.

4.13 Synthetic Data Generation

The compartment models in PKIN can be employed for creating data sets representing a perfect measurements with a certain acquisition protocol of the tissue and blood activities.

4.13.1 Synthetic Modeling Study for PKIN

PKIN always shows the model curve given the loaded input curve(s) and the configured regional kinetic model with the timing of the current study. The user may modify any of the defining parameters and observe the effect on the model curve, which represents the expected PET measurement. With the **Create Synthetic KM Study** facility well-defined and smooth TACs and blood curves can be generated which represent an ideal acquisition.

Synthetic Modeling Study Generation

1. Define a suitable kinetic model (compartment model, parameter values) in all regions.

2. Define a suitable input curve model, for instance a smooth curve fitted to the actual input curve.

3. Select the entry **Synthetic KM Study** in the **Kinetic** menu. A dialog appears showing the blood models and the model curve of the current region.
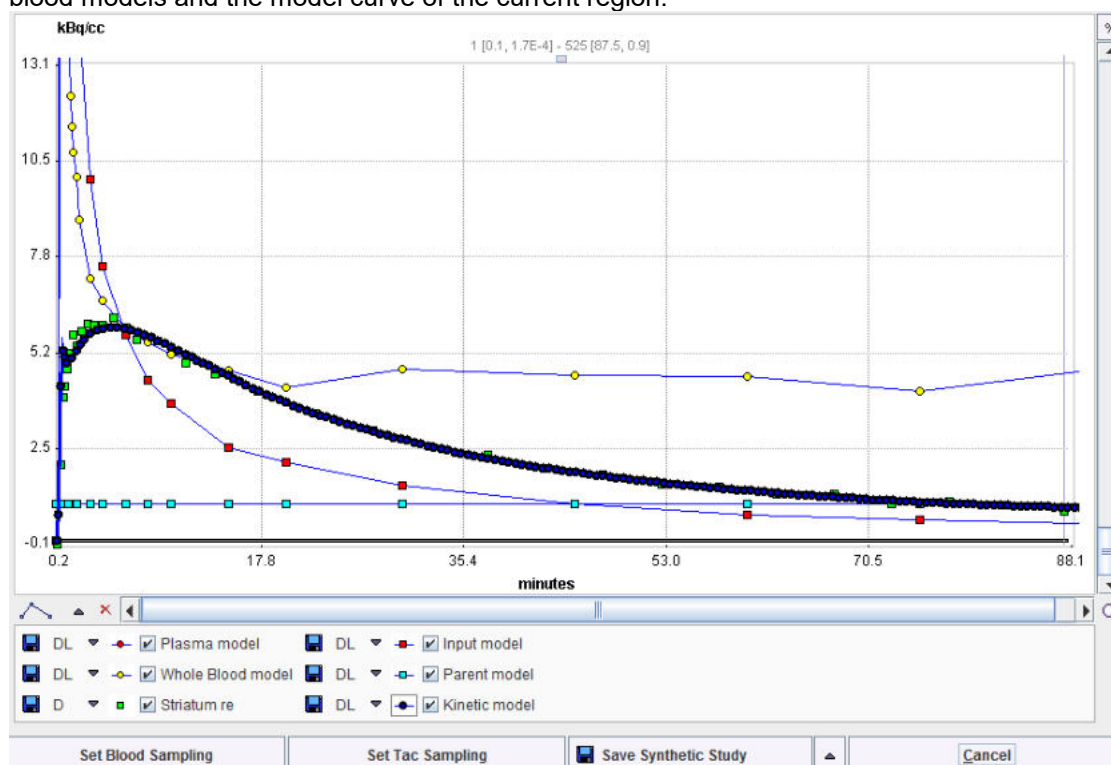
4. Initially all curves have the original sampling times. To modify sampling, use the buttons **Set Blood Sampling** and **Set Tac Sampling**. For instance, very fine sampling allows to generate smooth curves for publication or simulation purposes.

5. When **Save Synthetic Study** is activated, all regional TACs are recalculated with the current sampling, the old measurements are replaced by the values of the model curve, the original blood values are replaced by the values calculated with the current blood models, and the data

is saved in a file specified by the user. Then, the original data are shown again. As a convenience for adding the generated data set there is the button **Save & Append as new Study** available underneath:

6. Finally, to see and work with the synthetic study, load the created file. The synthetic model curves are now the measured TACs, and the resampled blood curves have the **Lin. Interpolation** model associated. So any underlying model of the blood curve (which has been used for synthetic model calculation) gets lost. This may cause small deviations between the calculated model curve and the saved synthetic TAC, depending on the density of blood sampling.

4.13.2 Synthetic Imaging Study for PXMOD Tests

Create Synthetic PXMOD Study is an extension of the **Create Synthetic KM Study** approach. The idea is that synthetic model curves can be generated for many different "tissues", ie. combinations of model parameters, at once. These curves are compiled into images, so that a synthetic study is generated which has a different combination of model parameters in each pixel.

For instance, TACs can be simulated by loading a .km file, selecting the 2-tissue compartment model and using the parameter ranges

Parameter	From	To
K_1	0.05	0.1
k_2	0.05	0.25
k_3	0.02	0.04
k_4	fixed to 0.05	

To enter these parameter ranges select **Create Synthetic PMXOD Study** from the **File** menu. The following dialog appears showing the parameters of the current model.
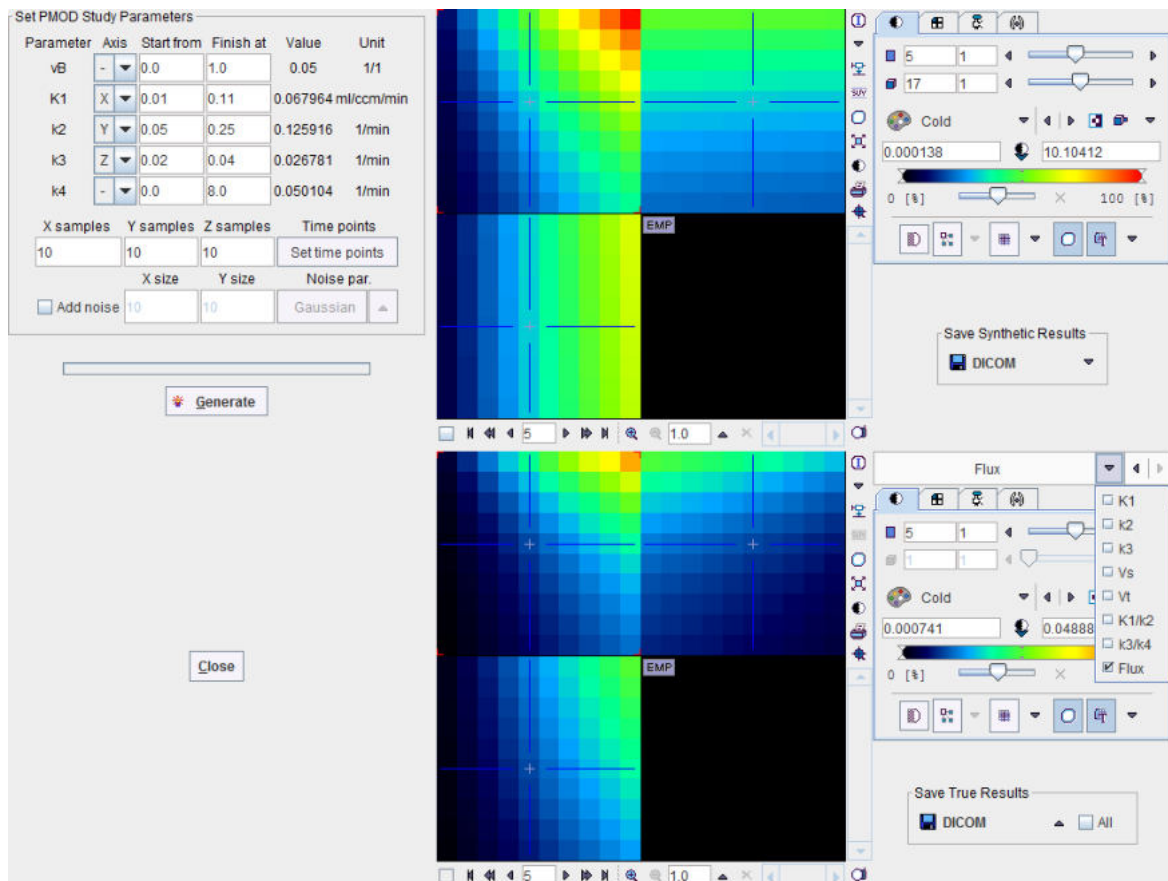
To define the synthetic study the following configurations must be set:

- Which parameters are varied along the **X**, **Y**, and **Z** axis (**Axis** selection),
- the value ranges of the varied parameters (**Start from**, **Finish at**),
- the number of parameter increments to cover the ranges (**X**, **Y**, **Z samples**),
- the acquisition times; initially the times of the loaded .km study are used, but they can be changed using the **Set time points**.

With **Generate** the model curves of all parameter combinations are generated and the data arranged as a 4-dimensional study. This synthetic study, which is suitable for pixel-wise modeling, is shown in the upper image display. In the example above the interpolation has been disabled to show the 10x10 layout of parameter combinations in plane. Use the **Save Synthetic Results** button to save the study in any supported output format.

The lower image display contains the true parameter images. These generation parameters can be saved using the **Save True Results** button. They can serve as the reference for the analysis of the outcome from a pixel-wise analysis of the synthetic study.

4.14   Modeling in Batch Pipeline

The PKIN models can be applied as part of a processing pipeline. For instance, a dynamic PET series can be motion corrected, an atlas fitted to the data and the regional TACs calculated which are then fitted by a model.

Association of Blood Components to Dynamic PET

For blood-based models the related information such as input curve, whole blood curve, and the parent fraction of an dynamic PET must be specified. This requires that the data resides in a PMOD database and uses the "association" concept which allows defining relationships between data elements.

For instance, the whole-blood curve is specified as follows. In the **Patients** list of the database browser select the patient, and in the **Series** list the dynamic PET. Next, activate the association list as illustrated below and select the **Associate Whole blood** entry.
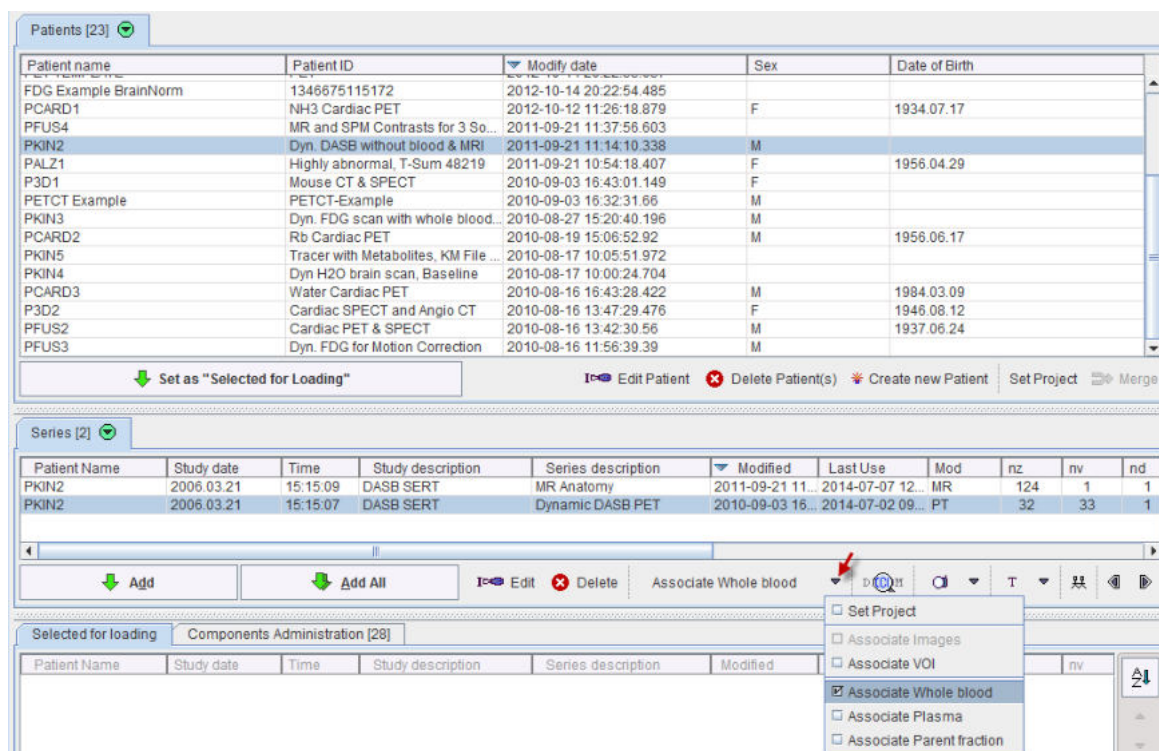
A component browser appears which is used to select the whole-blood curve. The same procedure is repeated for the input curve with the **Associate Plasma** entry, and if applicable with the **Associate Parent fraction**. From then on the roles of the blood curves is established, and selection of the dynamic PET is sufficient for modeling purposes.

Kinetic Modeling External Tool

Please refer to the *PMOD Base Tool Users Guide* for general explanations about setting up batch pipe processing. A modeling stage can be included by means of the **Kinetic Modeling** external tool which has the interface illustrated below.
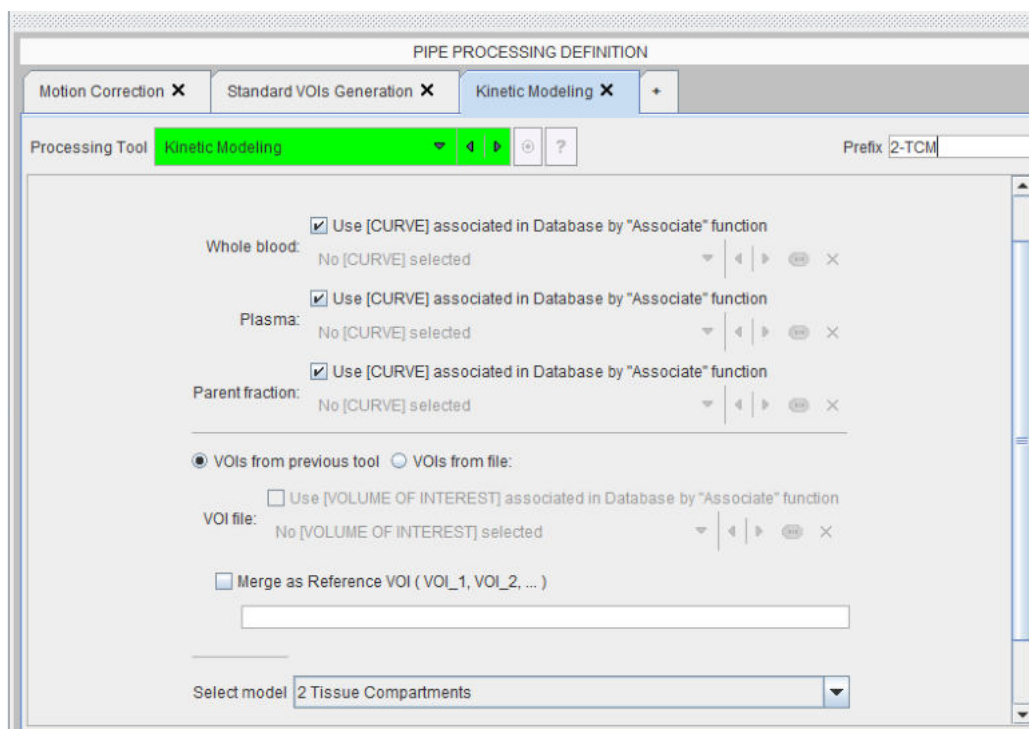
For blood-based models the whole-blood, plasma and parent fractions have to be specified. Unless data of the same study is processed multiple times with the same blood data, the associations have to be used for a general specification. With **VOIs from previous tool** the VOI definitions produced by the pipeline will be applied. Again, **VOIs from file** can only be applied wen processing the same data multiple times, or if the images have been normalized to a standard space.

For reference tissue models the reference TAC can be generated by combining a set of VOIs. The set has to be specified in a comma-separated list such a **Cerebellum_l,Cerebellum_r**, or using wildcards such as **Cerebellum***.

Finally, the tissue model to be fitted to each regional TAC can be chosen from the **Select model** list.

5   PKIN for Regional Parametric Mapping (option)

PXMOD is the main PMOD tool for parametric mapping and provides a streamlined workflow for the data analysis. However, the modeling incorporated in PXMOD features a limited set of models and is not aimed at detailed interactive modeling of TACs from individual pixels. PKIN offers an alternative for generating parametric maps of limited image sub-volumes, leveraging interactive modeling with the full model set as described below. For instance, the heterogeneity of a tumor might be investigated using the PKIN-based parametric mapping approach.

Note: The use of this functionality requires that the PXMOD Tool has been licensed in addition to PKIN.

5.1   Data Transfer for Parametric Mapping in PKIN

In order to use parametric mapping in PKIN, the dynamic data have to be loaded in the PVIEW tool, VOIs outlined, and then the transfer to PKIN started as illustrated below. As PKIN can only handle a limited number of TACs, the default **Maximal number of TACs** is set to 10000, but can be changed.
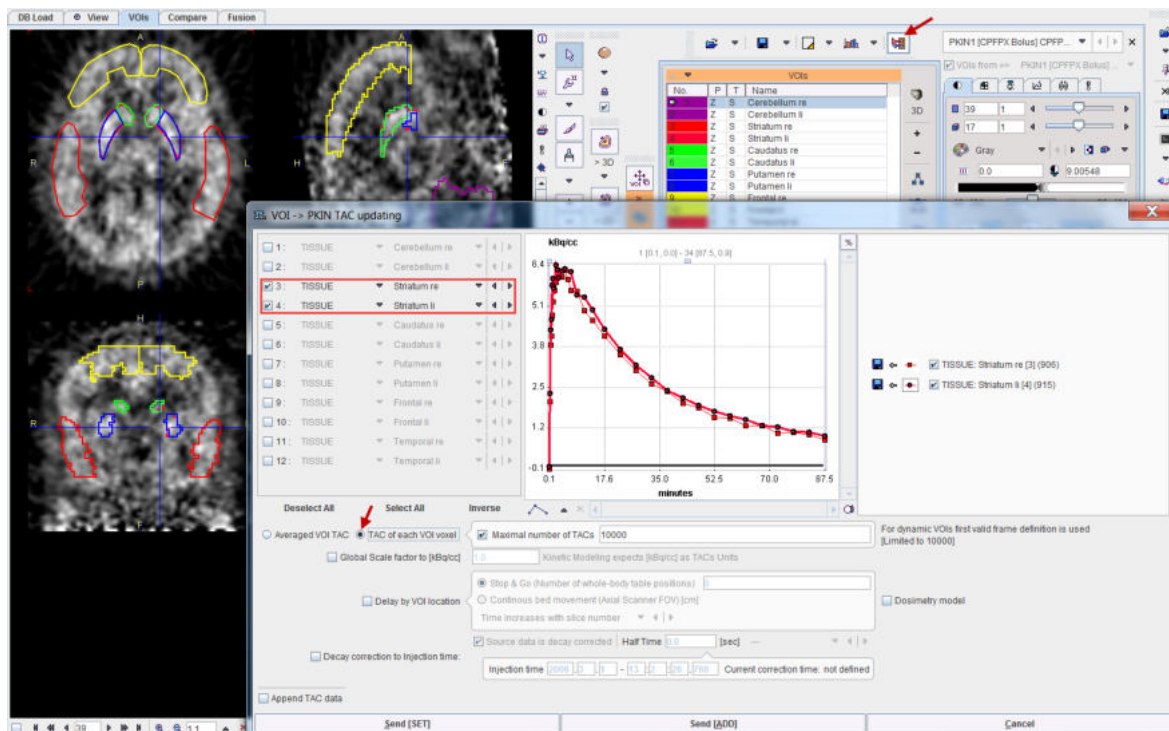
Please select only the relevant VOIs in the list to the left. The VOI average TACs are shown in the curve area, with the number of included voxels indicated in brackets in the list to the right. Activate **TAC of each VOI voxel**, and then transfer the data with **Send [SET]** to create a new PKIN workspace, or **Send [ADD]** to use the selected PKIN workspace.

If no blood information is available for modeling, an average TAC from a reference VOI will be needed. It is recommended transferring it separately as an average TAC by calling the transfer window again, this time only selecting the reference VOI, enabling **Averaged VOI TAC**, enabling **Append TAC data** and finally activating **Send [ADD]**.

Important: The image has to remain loaded in the PVIEW tool during parametric mapping in PKIN.

5.2 Voxel-wise TAC modeling in PKIN

After the transfer from the PVIEW tool the voxel-wise TACs are arranged in the **Region** list labeled with the VOI name followed by the voxel coordinate in the image. As for average TACs, the blood and plasma data have to be loaded, or a reference approach used.
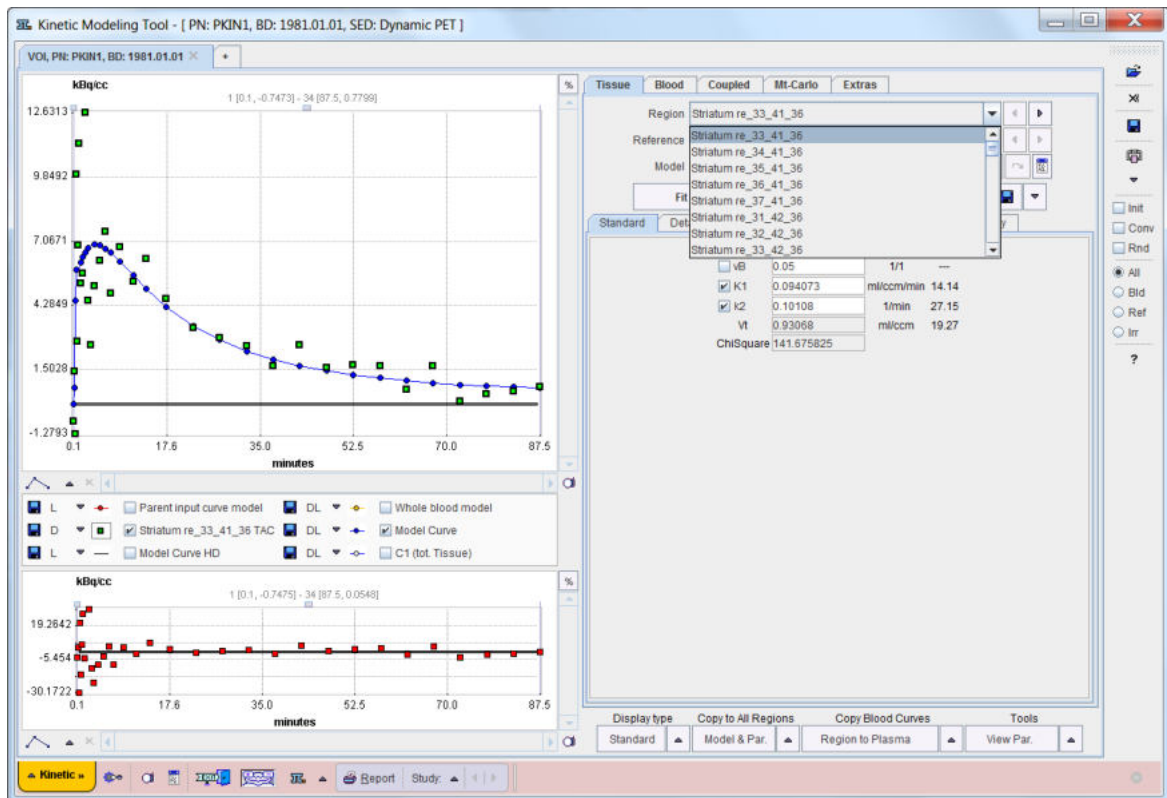
The whole PKIN functionality is then available for modeling. For instance, a few TACs can be averaged, [102] a 1-tissue compartment model fitted as illustrated, propagated to all TACs using **Copy to All Regions** entry **Model & Pa**r, and fitted with **Fit all regions**.

5.3 Parametric Mapping Interface

Select the entry **Create Parametric Maps** in the **Kinetic** menu in order to generate parametric maps from model parameters. Note that this entry is only active when a voxel-wise TAC transfer from PVIEW has been performed.
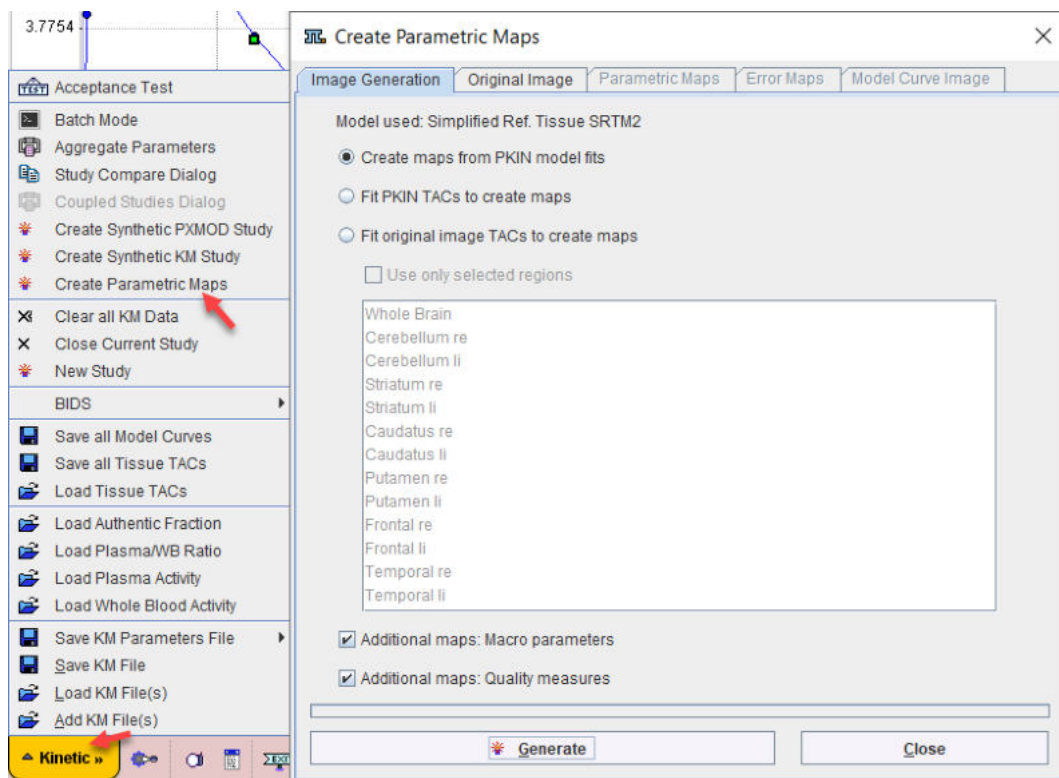
The dialog window offers three methods on the **Setup** panel.

Create maps from PKIN model fits	This method uses the results of the existing model fits in the PKIN workspace to generate the parametric maps.
Fit PKIN TACs to create maps	This method is the same as above, but first a model fit is performed in all regions using the model configured in the selected region.
Fit original image TACs to create map	This method is independent from the TAC contents in PKIN. It will use the model configured for the active region and fit it to the TACs of all voxels within the selected regions if **Use only selected regions** is enabled, and in the whole image volume otherwise. Note that the time required depends on the number of voxels to be fitted.
Additional maps: Macro parameters	Supports the creation of parametric maps from all the macro parameters of the model.
Additional maps: Quality measures	Supports the creation of parametric maps from all quality measures of the fit.

The **Generate** button starts processing with the selected method, resulting in images on the tabs **Parametric Maps**, **Error Maps** and **Model Curve Image**. Note the synchronization between the images on the various panels and the **Region** selected in the PKIN interface as described below[113].

Note: If average TACs were transferred, **Create Parametric Maps** can also be executed. All the settings described are applicable, but the parametric maps will consist of a single value in each region, the regional result.

5.3.1 Original Image Panel

The **Original Image** tab shows the image that was used for transferring the voxel-wise TACs, together with the VOIs. Besides providing reference for existing maps, it supports an interactive mode of fitting the TACs in voxels of interest.
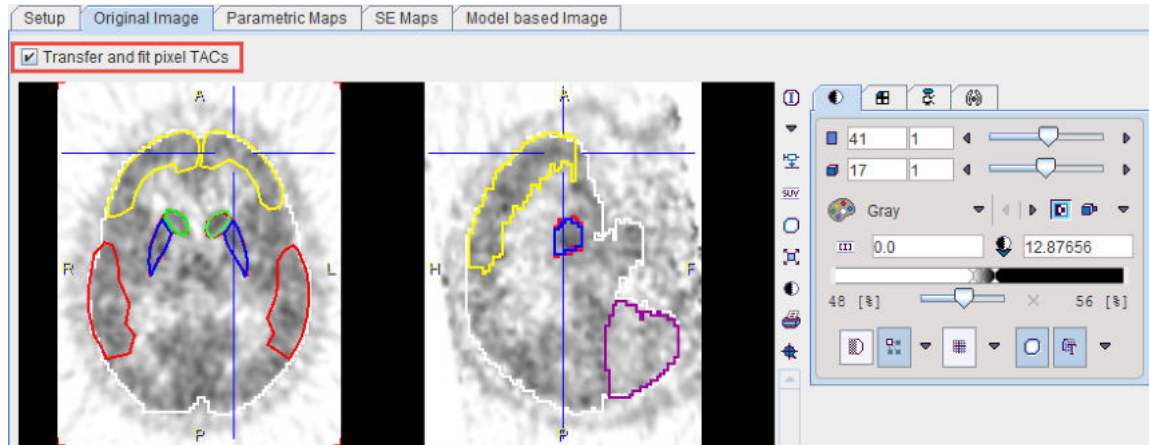
Once the **Transfer and fit pixel TACs** option has been enabled, the following happens when clicking into the image:

- The TAC of the voxel is transferred to PKIN and a new entry in the **Region** list is created,
- the model of the previously active region is fitted to the TAC,
- and the resulting parameters are added in the image on the **Parametric Maps** panel.

The example below shows the **Vt** map after clicking at 3 voxels in the frontal area.
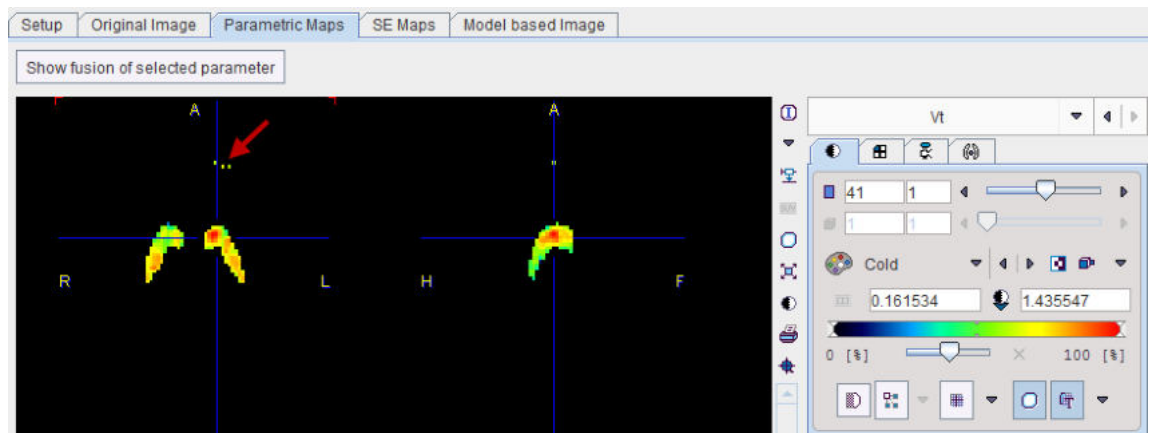
5.3.2 Parametric Maps Panel

The **Parametric Maps** panel shows the results from the voxel-wise fits as parametric images, with the selection between the different model parameters in the upper right.
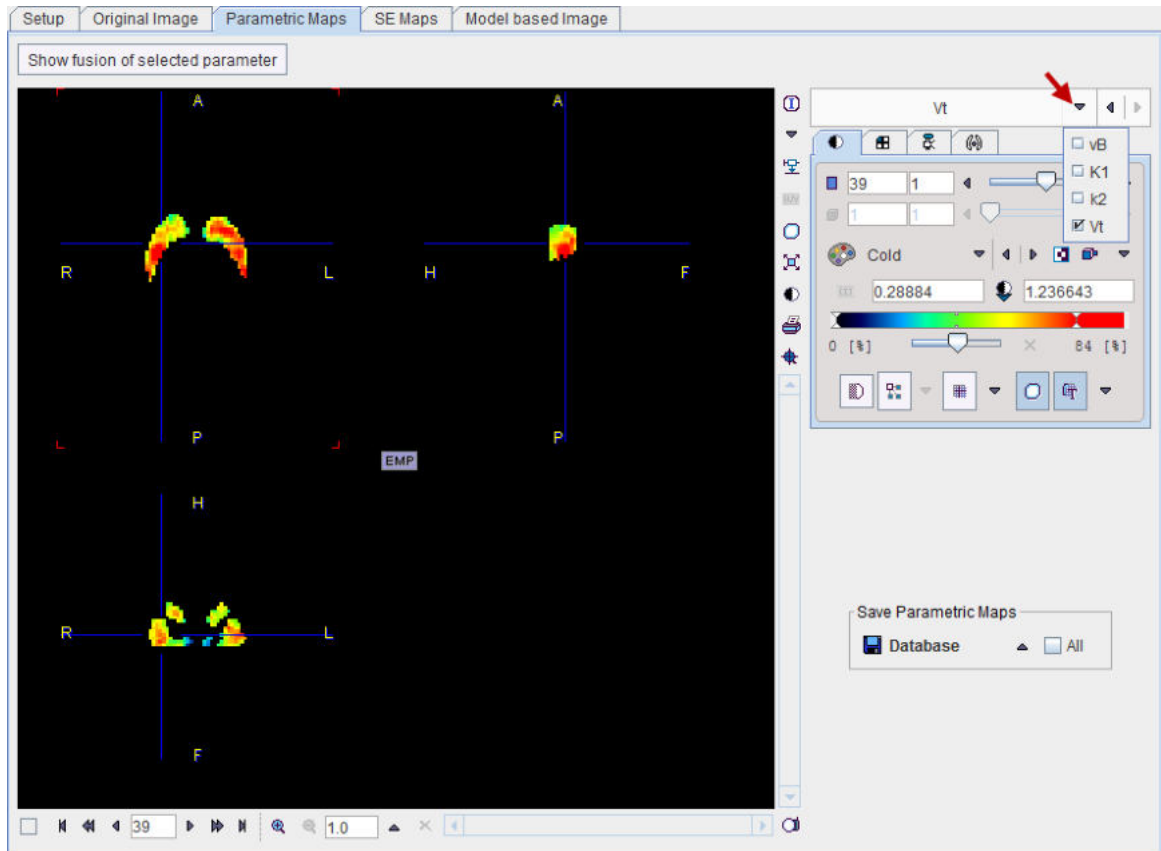
Save Parametric Maps allows saving the currently selected map, or **All** at once. **Show fusion of selected parameter** opens a dialog window showing the parametric map on top of the dynamic images.
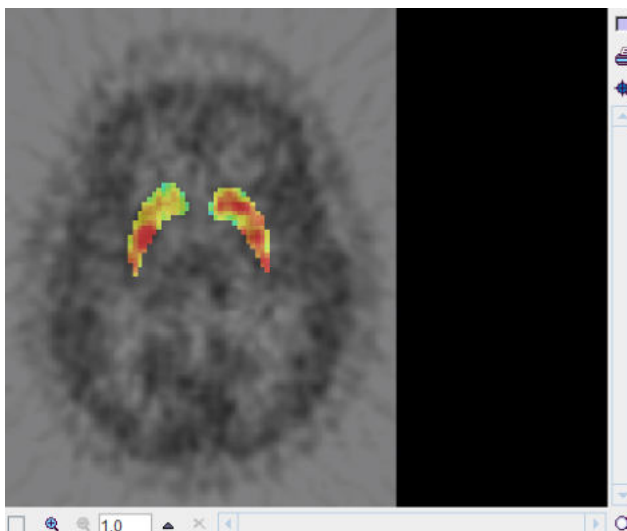
Fitting Inspection

If the parametric map has been produced from curves in the PKIN interface, the fit in the individual voxels can be inspected in detail. When clicking at voxels in a parametric map the **Region** in the main PKIN interface is switched to the corresponding entry, and the curve panel shows the TAC of the voxel with the model curve.
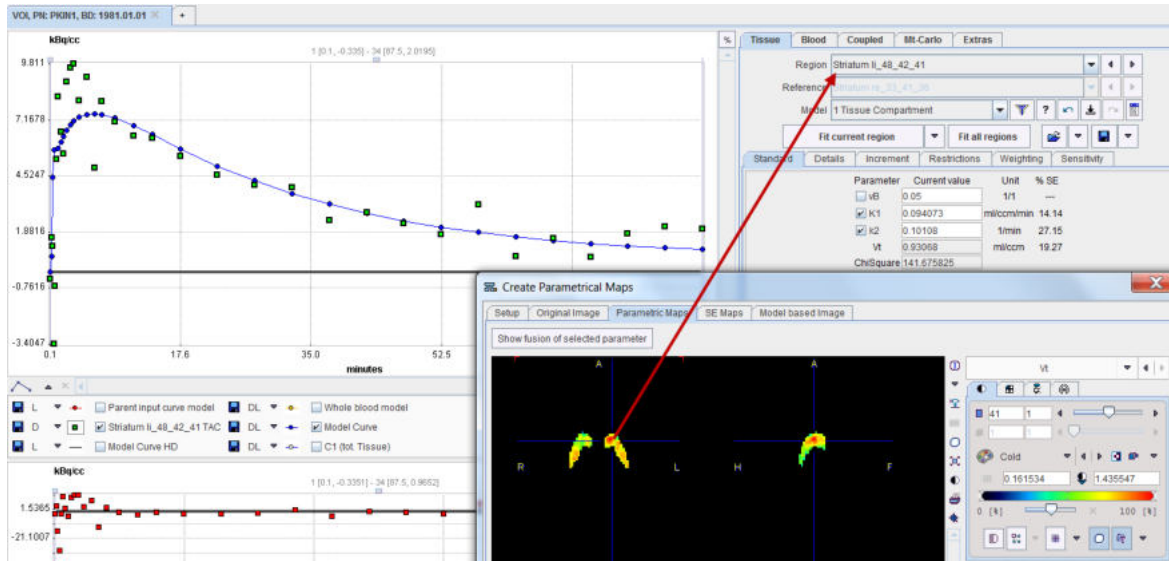
5.3.3 SE Maps Panel

The **Error Maps** panel shows the % standard error of the corresponding parameters on the **Parametric Maps** panel.
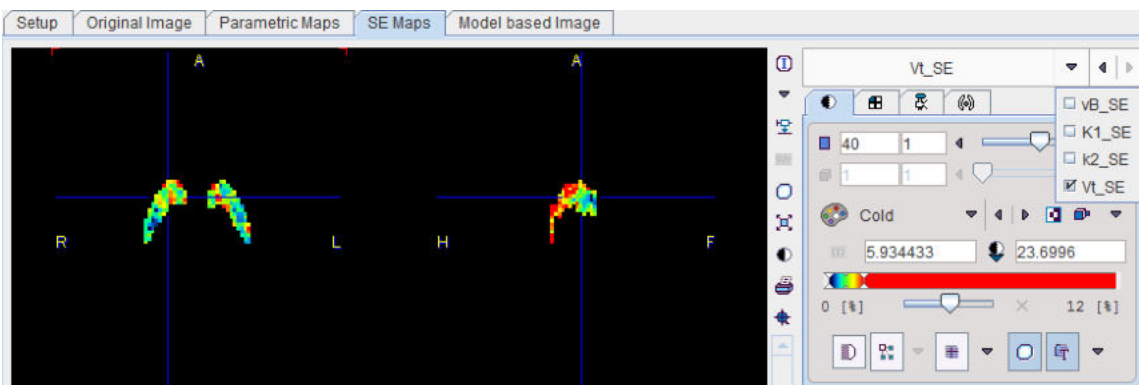
5.3.4 Model based Image Panel

The last panel contains a dynamic image series which is constructed from the fitted model curves. It can be saved via **Save Model Image** for other uses such as constructing digital phantoms or as input into other parametric mapping programs.
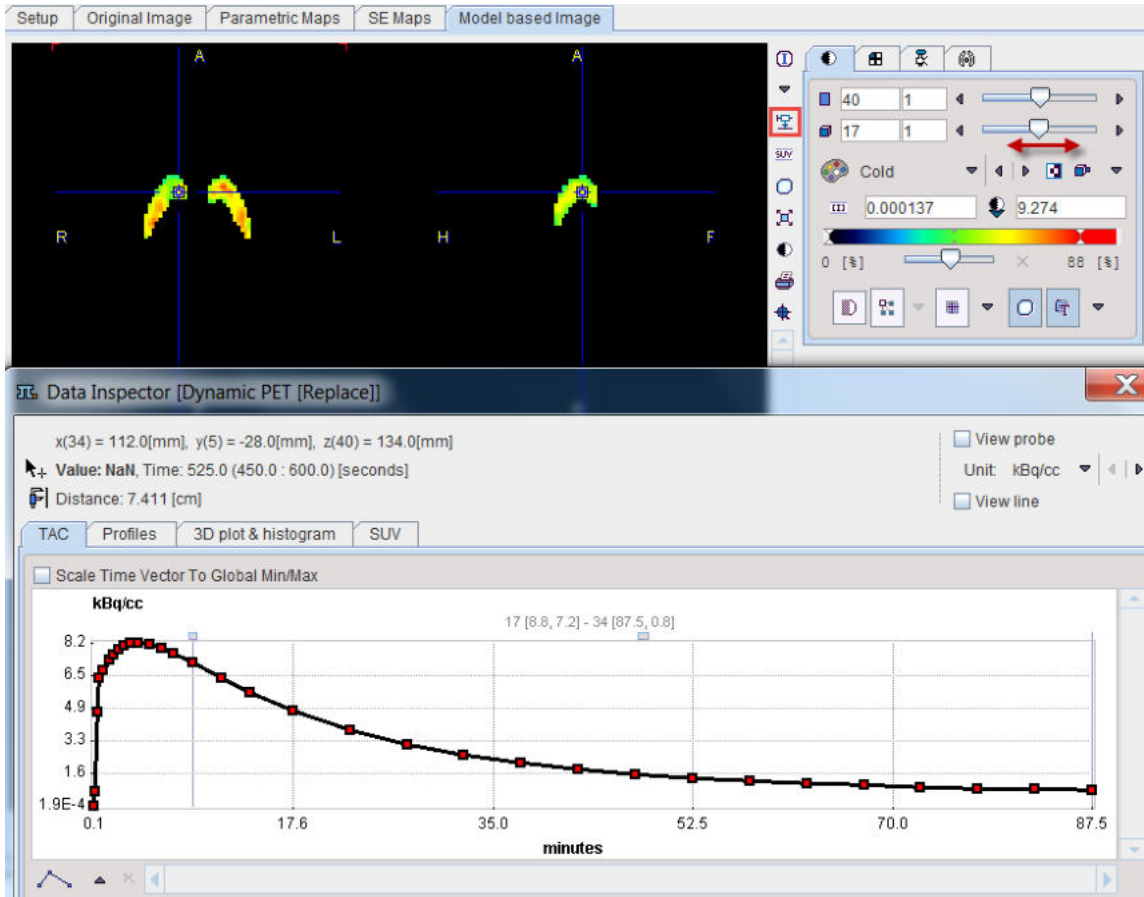
6   PKIN Reference

PKIN implements different types of models with somewhat different properties.

1. Compartment Models require an input curve for the calculation of the expected concentrations in the different compartments. Most of them also support a blood spillover correction term.

2. Reference models do not use explicit blood information. Rather, a reference TAC is specified which must satisfy specific criteria. The reference TAC is used to calculate the response in the tissue of interest.

3. Non-compartment models perform different types of analyses which are not based on a compartment structure of the model. Most of them use the input curve.

> **Note:** It is assumed that all data used has been **decay corrected** to the same time point.

6.1   Compartment Models

6.1.1   List of PKIN Compartment Models

PKIN features a comprehensive set of compartment models as listed below. The number of tissue compartments ranges from 1 to 3. There are different variants of the same model structure, so that prior information can be entered easily, and that coupling of physiologic parameters across region is possible.

For instance, the 2-tissue compartment model has the standard parameters K_1, k_2, k_3, k_4. An equivalent description is by the parameters K_1, K_1/k_2, k_3, k_4. The advantage is, that the K_1/k_2, represents the distribution volume of the non-displacement compartment in tissue (free and non-specifically bound tracer), which can often be assumed to be the same across different tissues. Therefore, K_1/k_2 can be included as a common parameter in a coupled fit, hereby reducing the number of fitted parameters and thus potentially improving the identifiability of all.

Model Name	Description
1-Tissue Compartment [119]	Most basic compartment model with the plasma compartment and one tissue compartment.
2-Tissue Compartments [119]	Compartment model with the plasma compartment and two sequential tissue compartments. Often used for receptor studies.
FDG-2 Tissue Compartments [119]	The 2-Tissue compartment model including the plasma glucose and the lumped constant to calculate the metabolic rate of glucose.
2-Tissue Compartments, K1/k2 [119]	The same model as the 2-Tissue compartment model, except that K_1/k_2 is used as a model parameter instead of k_2. This facilitates coupled fitting.
2-Tissue Compartments, K1/k2 &Vs [119] 2-Tissue Compartments, K1/k2 &Vt [121]	The same models as the 2-Tissue compartment model, except that K_1/k_2 and the specific or total distribution volumes are used as model parameters instead of k_2 and k_4. This facilitates coupled fitting and the easy generation of synthetic model curves.
2-Tissue compartments, Linear Least Squares [123]	2-Tissue compartment model solved by the Linear Least Squares method.

Parallel 2-Tissue Compartments [124]	2-Tissue compartment model with each compartment exchanging independently with blood.
2-Tissue Compartments, k5 [125]	2-Tissue compartment model with an efflux from the last compartment.
2-Tissue Compartments, Bmax [125]	Non-linear 2-Tissue compartment model for receptor tracer studies accounting for the saturation of receptor sites.
2-Tissue Compartments, K1/k2, Bmax [125]	Same model as above, but using K_1/k_2 as fitting parameter instead of k_2.
2-Tissue Compartments, vascular trapping [127]	2-Tissue compartment model with an additional endothelial trapping compartment.
Irreversible 2-Tissue [128] Irreversible 2-Tissue, Flux [129] Irreversible 2-Tissue, K1/k2, Flux [130]	In principle the same models as the 2-Tissue compartment model with $k_4=0$. The **Flux** variants allow using the influx as a fitting parameter, or as a fixed parameter set to the result of a Patlak analysis. When using K_1/k_2 also as a fitting parameter, coupled fitting can be employed.
3-Tissue Compartments [132]	Compartment model which separates free tracer in tissue from non-specific binding.
3-Tissue Compartments, K1/k2, Vs [132]	As above, but using but using K_1/k_2 and the specific distribution volume as fitting parameters.
3-Tissue Compartments, sequential [133]	Model with three sequential compartments originally developed for FDG uptake in skeletal muscle.
Flow & Dispersion [139]	Specific model for dynamic $H_2^{15}O$- PET Data with implicit deconvolution of the input curve dispersion
3-Tissue Compartments, Metabolites [134]	Extends the 2 tissue compartment model by a metabolite compartment with a second input curve of labeled metabolites from the plasma.
3-Tissue Compartments, Metabolites, K1/k2 [135] 3-Tissue Compartments, Metabolites, K1/k2, Vs [135]	As above, but using but using K_1/k_2 and the specific distribution volume as fitting parameters.
4-Tissue Compartments, Metabolites, K1/k2 [136]	Two parallel 2-compartment models for authentic ligand and metabolites, linked by a transfer constant between the non-specific compartments.
Triple-injection Protocol for Flumazenil [137]	During a single imaging study three injections are applied: hot ligand first, then cold ligand for displacement, then a mixture of cold & hot ligand. The individual receptor parameters can be estimated.

6.1.2   1-Tissue Compartment Model

The 1-Tissue Compartment Model only separates tissue uptake and washout. All tracer in tissue is included in a single compartment C_1.
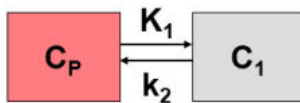
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t)$$

with input curve $C_p(t)$, tissue concentration $C_1(t)$, uptake rate constant K_1 [ml/ccm/min] and clearance rate constant k_2 [1/min].

Operational Model Curve

$$C_{Model}(t) = (1 - vB) C_1(t) + vB C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the three fitable parameters **vB**, **K1**, **k2**. Often, **vB** is fixed at a physiologic value of 3-5%.

6.1.3   2-Tissue Compartment Model

The 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] and k_4 [1/min] describe the exchange between the tissue compartments. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 specifically bound tracer.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB) (C_1(t) + C_2(t)) + vB C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 5 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**. Usually, v_B is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters. An alternative is to fit v_B with a TAC from a big representative VOI, and fix it for the TACs from smaller VOIs. For irreversible tracers with trapping in the second compartment, k_4 is fixed: **k4**=0. Please inspect the **%SE** standard error to get information about the reliability of the parameter estimates.

Alternative Models with VND and VS Fit Parameters

There are two alternative models available which have the same structure but use distribution volumes as fit parameters. The advantage of the reformulation is that in some situations distribution volumes can be assumed to be common among regions and estimated by a coupled fit, or they might already be known and can thus be fixed at a prior value.

6.1.4 2-Tissue Compartment Model, K1/k2

The 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] and k_4 [1/min] describe the exchange between the tissue compartments. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 specifically bound tracer.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using K_1/k_2 instead of k_2

The **2-Tissue Compartment Model, K1/k2** model variant uses **K1/k2** as a fitting parameter instead of **k2**. K_1/k_2 represents the distribution volume V_{ND} of the non-displaceable compartment C_1. The advantage of this formulation is that in some situations V_{ND} can be assumed to be common among regions and estimated by a coupled fit. Alternatively, V_{ND} might already be known and can thus be fixed at a prior value. The other four fitting parameters **vB**, **K1**, **k3**, **k4** are the same as for the **2-Tissue Compartment Model**.

6.1.5 2-Tissue Compartment Model, K1/k2, Vs

The 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2. K_1 [ml/ccm/min] and k_2 [1/min]

are the uptake and clearance rate constants, whereas k_3 [1/min] and k_4 [1/min] describe the exchange between the tissue compartments. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 specifically bound tracer.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using K_1/k_2 and Vs

This **2-Tissue Compartment Model, K1/k2, Vs** model variant uses **K1/k2** and **Vs** as fitting parameters instead of k_2 and k_4. V_S ($=K_1/k_2*k_3/k_4$) represents the distribution volume of the specific compartment C_2. This formulation has particular advantages for the generation of synthetic data with predefined distribution volumes. The other three fitting parameters **vB**, **K1**, and **k3** are the same as for the **2-Tissue Compartment Model**.

6.1.6　2-Tissue Compartment Model, K1/k2, Vt

The 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] and k_4 [1/min] describe the exchange between the tissue compartments. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 specifically bound tracer.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using K_1/k_2 and Vt

This **2-Tissue Compartment Model, K1/k2, Vt** model variant uses **K1/k2** and **Vt** as fitting parameters instead of k_2 and k_4. V_t (=K_1/k_2*(1+k_3/k_4)) represents the total distribution volume of tracer in tissue. This formulation has particular advantages for the generation of synthetic data with predefined distribution volumes. The other three fitting parameters v_B, K_1, and k_4 are the same as for the **2-Tissue Compartment Model**.

6.1.7 FDG 2-Tissue Compartment Model

The 2-tissue compartment model for FDG has the same structure as the standard model.
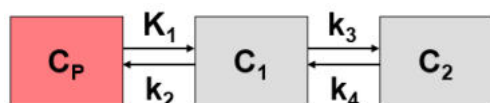
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with FDG concentration of in arterial plasma $C_p(t)$, FDG concentration $C_1(t)$ and phosphorylated FDG (FGD-6-P) concentration $C_2(t)$ in tissue. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] represents phosphorylation by hexokinase and k_4 [1/min] dephosphorylation.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 5 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**. Usually, **vB** is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters, and dephosphorylation is so slow that k_4 is fixed **k4**=0.

FDG-specific Results

The FDG model has two additional input parameters, the lumped constant (**LC**) and the plasma glucose concentration (**PG** [mmol/l]). In combination with the estimated K_1, k_2, and k_3 parameters they allow calculating the metabolic rate of glucose MRGlu

$$MRGlu = \frac{PG}{LC}\frac{K_1 k_3}{k_2 + k_3}$$

Note that the **LC** and **PG** values are maintained when switching back and forth with the **Patlak** model, if the **Model conversion** option in the **Extras** panel is enabled.

6.1.8 2-Tissue Compartment Model, Linear Least Squares Method

In addition to uptake and washout the model handles two exchanging compartments C_1 and C_2 in tissue.
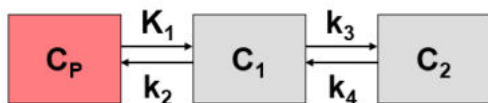
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

With linearized solutions, the differential equations are integrated twice on both sides, substitutions performed and finally rearranged. This can be done in different ways. The current model uses the derivation of Cai et al. [1], equation (6):

$$C_{Model}(t) = P_1 C_B(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 \int_0^t \int_0^\tau C_P(s)ds d\tau + P_4 \int_0^t C_{PET}(\tau)d\tau + P_5 \int_0^t \int_0^\tau C_{PET}(s)ds d\tau$$

with input curve $C_p(t)$, the concentration $C_B(t)$ of tracer in whole blood, and the tissue curve to be fitted $C_{PET}(t)$.

Parameter Fitting

The multi-linear operational equation can be solved in a least squares sense in one step using a singular value decomposition method. From the resulting 5 coefficients $P_1, .. , P_5$ the target parameters can be calculated as follows:

$$vB = P_1 \qquad k_3 = -(k_2 + k_4 + P_4)$$

$$K_1 = \frac{P_1 P_4 + P_2}{1 - P_1} \qquad k_4 = \frac{-P_5}{k_2}$$

$$k_2 = -\frac{P_1 P_5 + P_3}{P_1 P_4 + P_2} - P_4$$

Recommended Use of the Linear Least Squares Method

The advantages of the linearized approach are fast computation, a well-defined solution, and no problem with local minima. However, it is well known that the method is susceptible to bias, and that small TAC perturbations can cause large changes of the parameter estimates. Therefore it is recommended that the **Linear Least Squares** model is only used for getting a quick solution which is further refined by the iterative methods. In fact, if **Parameters Initialization** option is configured in the **Extras** panel, the initial starting parameters of the compartment models are obtained by the **Linear Least Squares** method.

Implementation Notes

The model works as follows for different model configurations:

- Irreversible model: if **k4** is disabled from fitting, the program automatically sets **k4** = 0 and uses a linearized equation which is modified accordingly.

- 1-tissue compartment model: if **k3** is disabled from fitting, the program automatically sets **k3** = **k4** = 0 and uses a modified equation.
- In all configurations the **vB** parameter can optionally be disabled from fitting and fixed at a specific user-defined value.

Reference

1. Cai W, Feng D, Fulton R, Siu WC: Generalized linear least squares algorithms for modeling glucose metabolism in the human brain with corrections for vascular effects. Comput Methods Programs Biomed 2002, 68(1):1-14.

6.1.9   Parallel 2-Tissue Compartment Model

This model was developed for the analysis of renal PET data [1]. It consists of two parallel tissue compartments, C_1 representing non-specific uptake, and C_2 specific binding.
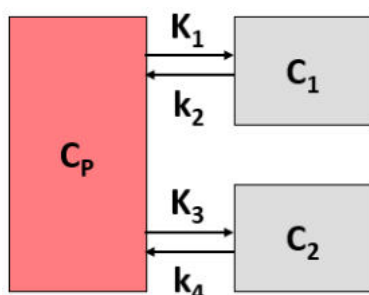
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 \, C_P(t) - k_2 \, C_1(t)$$
$$\frac{dC_2(t)}{dt} = K_3 \, C_P(t) - k_4 \, C_2(t)$$

with input curve $C_p(t)$, concentration $C_1(t)$ in the first and concentration $C_2(t)$ in the second compartment. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants of $C_1(t)$, K_3 [ml/ccm/min] and k_4 [1/min] of $C_2(t)$ respectively. In the analysis of Gulaldi et al [1] C_1 represents non-specifically bound tracer in tissue and C_2 represents specifically bound tracer.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)\,(C_1(t) + C_2(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.
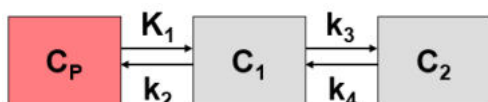
Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **k2**, **K3**, **k4**. Usually, vB is fixed at a physiologic value to reduce the number of fitted parameters. In [1] vB was fixed at 0.15, which is used as the parameter default.

Reference

1. Gulaldi NC, Xia J, Feng T, Hong K, Mathews WB, Ruben D, Kamel IR, Tsui BM, Szabo Z: Modeling of the renal kinetics of the AT1 receptor specific PET radioligand [11C]KR31173. Biomed Res Int 2013, 2013:835859. DOI

6.1.10 2-Tissue Compartment Model, k5

In addition to uptake and washout the model handles two exchanging compartments C_1 and C_2 in tissue, as well as an efflux from C_2.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - (k_4 + k_5) C_2(t)$$

with input curve $C_p(t)$, concentration $C_1(t)$ in the first and concentration $C_2(t)$ in the second compartment. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] and k_4 [1/min] describe the exchange between the tissue compartments. The typical interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 represents specifically bound tracer.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

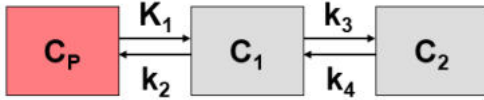with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**, **k5**. Usually, vB is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters. Per default, **k4**=0 is fixed to model an efflux from the specific compartment rather than an exchange with the non-displaceable compartment.

6.1.11 2-Tissue Compartment Model, Bmax

The saturable receptor-ligand model includes two tissue compartments. C_1 represents the non-displaceable tissue compartment with free and non-specifically bound tracer, and C_2 tracer bound to the target receptors. The model accounts for a saturation of receptor sites due to low specific activity S_{act} of the injected tracer. In this situation, k_3 is given by $k_{on}(B_{max}-C_2(t)/S_{act})$, and is therefore time-dependent. B_{max} is the total receptor concentration, k_{on} the bi-molecular association rate, and k_4 the dissociation rate constant k_{off}.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t) - k_{on} C_1(t)\left(B_{max} - \frac{C_2(t)}{S_{act}}\right) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_{on} C_1(t)\left(B_{max} - \frac{C_2(t)}{S_{act}}\right) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **k2**, **k3on**, **k4**, **Bmax**. Due to the high number of parameters, it is difficult to use the model for actual fitting. However, it may be valuable for generating synthetic data and assessing the effect of model simplification.

Alternative Model with K1/k2 Fit Parameter

There is an alternative **2-Tissue Compartment Model, K1/k2, Bmax** model available which has the same structure but uses K_1/k_2 as a fitting parameter instead of k_2. K_1/k_2 represents the distribution volume V_{ND} of the non-displaceable compartment C_1. The advantage of this formulation is that in some situations V_{ND} can be assumed to be common among regions and estimated by a coupled fit. Alternatively, V_{ND} might already be known and can thus be fixed at a prior value.

6.1.12 2-Tissue Compartment Model, K1/k2, Bmax

The saturable receptor-ligand model includes two tissue compartments. C_1 represents the non-displaceable tissue compartment with free and non-specifically bound tracer, and C_2 tracer bound to the target receptors. The model accounts for a saturation of receptor sites due to low specific activity S_{act} of the injected tracer. In this situation, k_3 is given by $k_{on}(B_{max}-C_2(t)/S_{act})$, and is therefore time-dependent. B_{max} is the total receptor concentration, k_{on} the bi-molecular association rate, and k_4 the dissociation rate constant k_{off}.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - k_2 C_1(t) - k_{on} C_1(t)\left(B_{max} - \frac{C_2(t)}{S_{act}}\right) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_{on} C_1(t)\left(B_{max} - \frac{C_2(t)}{S_{act}}\right) - k_4 C_2(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

This model alternative **2-Tissue Compartment Model, K1/k2, Bmax** uses **K1/k2** as a fitting parameter instead of **k2**. K_1/k_2 represents the distribution volume V_{ND} of the non-displaceable compartment C_1. The advantage of this formulation is that in some situations V_{ND} can be assumed to be common among regions and estimated by a coupled fit. Alternatively, V_{ND} might already be known and can thus be fixed at a prior value. The other 5 fitable parameters **vB**, **K1**, **k3on**, **k4**, **Bmax** are the same as for the **2-Tissue Compartment Model, Bmax** model.

Due to the high number of parameters, it is difficult to use the model for actual fitting. However, it may be valuable for generating synthetic data and assessing the effect of model simplification.

6.1.13 2-Tissue Compartment Model with Vascular Trapping

This model has been developed by Rizzo et al. [1] for the analysis of [11C]-PBR28 uptake in the human brain. In addition to the compartments in the standard 2-tissue compartment model, a compartment C_{vasc} was introduced which represents slow binding of the tracer to the endothelium of the vasculature.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_{vasc}(t)}{dt} = K_b C_P(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB(C_B(t) + C_{vasc}(t))$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**, **Kb**. Usually, **vB** is fixed at a physiologic value of 3-5%. The default initial parameter values are the ones which were used for PBR28.

Reference

1. Rizzo G, Veronese M, Tonietto M, Zanotti-Fregonara P, Turkheimer FE, Bertoldo A. Kinetic modeling without accounting for the vascular component impairs the quantification of [(11)C] PBR28 brain PET data. J Cereb Blood Flow Metab. 2014;34(6):1060-9. DOI

6.1.14 2-Tissue Compartment Model with Vascular Binding

A model with vascular binding has been developed by Rizzo et al. [1] for the analysis of [11C]-PBR28 uptake in the human brain. In addition to the compartments in the standard 2-tissue compartment model, a compartment C_{vasc} was introduced which represents slow binding of the tracer to the endothelium of the vasculature. This variant allows for reversible endothelial binding. Additionally, K_1/k_2 was introduced as a fit parameter, allowing to reduce the number of fit parameters via regional parameter coupling.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_{vasc}(t)}{dt} = K_{b1} C_P(t) - k_{b2} C_{vasc}(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB(C_B(t) + C_{vasc}(t))$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **K1/k2**, **k3**, **k4**, **Kb1** and **kb2**. Usually, **vB** is fixed at a physiologic value of 3-5%. Where possible, the default initial parameter values are the ones which were used for PBR28.

6.1.15 Irreversible 2-Tissue Compartment Model

The irreversible 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2 where the tracer is trapped. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] describes the trapping. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 irreversibly bound or metabolized tracer.

An important parameter of an irreversible configuration is net influx rate K_i, the unidirectional uptake rate constant that incorporates both net inward transport and trapping of the tracer in tissue.

$$\text{Net influx} = K_i = \frac{K_1 k_3}{k_2 + k_3}$$

Another macroparameter "lambda*k_3" as been used in the context of enzymatic reactions, where k_3 is supposed to be proportional to enzyme concentration.

$$\lambda k_3 = (K_1 / k_2) k_3$$

Logan et al. [1] have shown in simulations that lambda*k_3 is preferable to k_3 alone in terms of bias and precision.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

with input curve $C_p(t)$.

Operational Model Curve

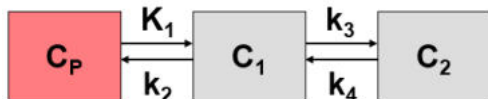$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 4 fitable parameters **vB**, **K1**, **k2**, **k3**, and calculates the macroparameter **Flux**. Usually, v_B is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters. An alternative is to fit v_B with a TAC from a big representative VOI, and fix it for the TACs from smaller VOIs.

Alternative Models with Flux Fit Parameter

There are two alternative models available which have the same structure but use the **Flux** as a fit parameter. The advantage of the reformulation is that the **Flux** can be calculated with the robust Patlak 168 model, and used as a fixed parameter in the compartment model fit.

Reference

1. Logan J, Fowler JS, Ding YS, Franceschi D, Wang GJ, Volkow ND, Felder C, Alexoff D: Strategy for the formation of parametric images under conditions of low injected radioactivity applied to PET studies with the irreversible monoamine oxidase A tracers [11C]clorgyline and deuterium-substituted [11C]clorgyline. J Cereb Blood Flow Metab 2002, 22(11):1367-1376. DOI

6.1.16 Irreversible 2-Tissue Compartment Model, Flux

The irreversible 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2 where the tracer is trapped. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] describes the trapping. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 irreversibly bound or metabolized tracer.

An important parameter of an irreversible configuration is net influx rate K_i, the unidirectional uptake rate constant that incorporates both net inward transport and trapping of the tracer in tissue.

$$\text{Net influx} = K_i = \frac{K_1 k_3}{k_2 + k_3}$$

Another macroparameter "lambda*k_3" as been used in the context of enzymatic reactions, where k_3 is supposed to be proportional to enzyme concentration.

$$\lambda k_3 = (K_1 / k_2) k_3$$

Logan et al. [1] have shown in simulations that lambda*k_3 is preferable to k_3 alone in terms of bias and precision.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.
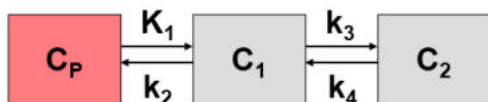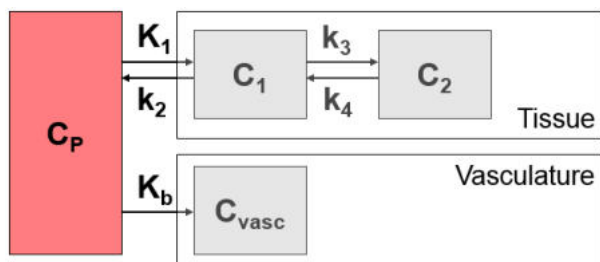
Parameter Fitting

The model includes the 4 fitable parameters **vB**, **K1**, **Flux**, **k3**, and calculates the **LambdaK3** macroparameter. Usually, v_B is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters.

Parameter Fitting using Flux instead of k_2

The **Irreversible 2-Tissue Compartment Model, Flux** model variant uses **Flux** as a fitting parameter instead of **k2**. The advantage of the reformulation is that the **Flux** can be calculated as a regression slope with the robust Patlak $\boxed{168}$ model, and used as a fixed parameter in the compartment model fit. If the Model Conversion $\boxed{51}$ option is enabled, the **Flux** will be copied when switching from the Patlak model to the **Irreversible 2-Tissue Compartment Model, Flux** model.

Reference

1. Logan J, Fowler JS, Ding YS, Franceschi D, Wang GJ, Volkow ND, Felder C, Alexoff D: Strategy for the formation of parametric images under conditions of low injected radioactivity applied to PET studies with the irreversible monoamine oxidase A tracers [11C]clorgyline and deuterium-substituted [11C]clorgyline. J Cereb Blood Flow Metab 2002, 22(11):1367-1376. DOI

6.1.17 Irreversible 2-Tissue Compartment Model, K1/k2, Flux

The irreversible 2-tissue compartment model separates tracer in tissue into two exchanging compartments C_1 and C_2 with a serial structure. The arterial plasma exchanges with the first tissue compartment C_1, which in turn exchanges with the second tissue compartment C_2 where the tracer is trapped. K_1 [ml/ccm/min] and k_2 [1/min] are the uptake and clearance rate constants, whereas k_3 [1/min] describes the trapping. The usual interpretation is that C_1 represents free and non-specifically bound tracer in tissue (non-displaceable compartment), and C_2 irreversibly bound or metabolized tracer.

An important parameter of an irreversible configuration is net influx rate K_i, the unidirectional uptake rate constant that incorporates both net inward transport and trapping of the tracer in tissue.

$$\text{Net influx} = K_i = \frac{K_1 k_3}{k_2 + k_3}$$

Another macroparameter "lambda*k_3" as been used in the context of enzymatic reactions, where k_3 is supposed to be proportional to enzyme concentration.

$$\lambda k_3 = (K_1 / k_2) k_3$$

Logan et al. [1] have shown in simulations that lambda*k_3 is preferable to k_3 alone in terms of bias and precision.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.
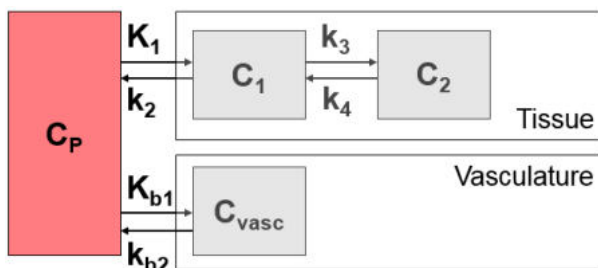
Parameter Fitting

The model includes the 4 fitable parameters **vB**, **K1/k2**, **Flux**, and calculates the **LambdaK3** macroparameter. Usually, v_B is fixed at a physiologic value of 3-5% to reduce the number of fitted parameters.

Parameter Fitting using K1/k2 and Flux instead of k_2 and k_3

The **Irreversible 2-Tissue Compartment Model, K1/k2, Flux** model variant uses **K1/k2** and **Flux** as fitting parameters instead of **k2** and **k3**. The advantage of the reformulation is that the **Flux** can be calculated as a regression slope with the robust Patlak 168 model, and used as a fixed parameter in the compartment model fit. If the Model Conversion 51 option is enabled, the **Flux** will be copied when switching from the Patlak model to the **Irreversible 2-Tissue Compartment Model, K1/k2, Flux** model. Similarly **K1/k2** will be copied when switching from a 2-Tissue compartment model. Another potential application is the use of coupled fitting 64 with a common **K1/k2** across regions.

Reference

1. Logan J, Fowler JS, Ding YS, Franceschi D, Wang GJ, Volkow ND, Felder C, Alexoff D: Strategy for the formation of parametric images under conditions of low injected radioactivity applied to PET studies with the irreversible monoamine oxidase A tracers [11C]clorgyline and deuterium-substituted [11C]clorgyline. J Cereb Blood Flow Metab 2002, 22(11):1367-1376. DOI

6.1.18 3-Tissue Compartment Model

This 3-tissue compartment model separates free tracer $C_1(t)$ and non-specifically bound tracer $C_3(t)$ in the non-displaceable compartment. K_1 and k_2 describe the exchange between arterial plasma and tissue, k_3 and k_4 between free and specifically bound tracer $C_2(t)$ in tissue, and k_5 and k_6 between free and non-specifically bound tracer.
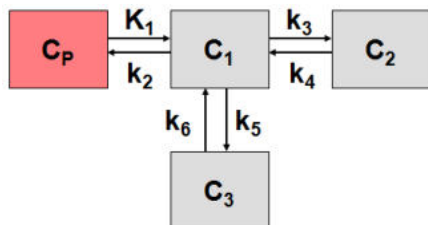
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3 + k_5)\, C_1(t) + k_4\, C_2(t) + k_6\, C_3(t)$$

$$\frac{dC_2(t)}{dt} = k_3\, C_1(t) - k_4\, C_2(t)$$

$$\frac{dC_3(t)}{dt} = k_5\, C_1(t) - k_6\, C_3(t)$$

with input curve $C_p(t)$.

Operational Model Curve
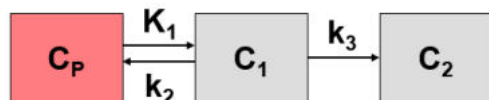
$$C_{Model}(t) = (1 - vB)\,(C_1(t) + C_2(t) + C_3(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model in principle includes the 7 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**, **k5**, **k6**, but reliable fitting cannot be achieved in practice. However, the model can be valuable for educational purposes and for generating simulation data.

6.1.19 3-Tissue Compartment Model, K1/k2, Vs

This 3-tissue compartment model separates free tracer $C_1(t)$ and non-specifically bound tracer $C_3(t)$ in the non-displaceable compartment. K_1 and k_2 describe the exchange between arterial plasma and tissue, k_3 and k_4 between free and specifically bound tracer $C_2(t)$ in tissue, and k_5 and k_6 between free and non-specifically bound tracer.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3 + k_5) C_1(t) + k_4 C_2(t) + k_6 C_3(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_3(t)}{dt} = k_5 C_1(t) - k_6 C_3(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t) + C_3(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using Distribution Volumes

This variant of the **3-Tissue Compartment Model** uses three distribution volumes as fitting parameters: the distribution volume of free tracer (**K1/k2**), of non-specifically bound tracer **Vns** (= $(K_1{}^*k_5)/(k_2{}^*k_6)$), and specifically bound tracer **Vs** (=$(K_1{}^*k_3)/(k_2{}^*k_4)$) instead of k_2, k_4 and k_6.

6.1.20 3-Tissue Compartment Model, Sequential

This model has been developed by Bertoldo et al. [1] for the analysis of FDG uptake in skeletal muscle. In this context C_1, C_2 and C_3 correspond to extracellular, intracellular and phosphorylated intracellular FDG. K_1 [ml/ccm/min] and k_2 [1/min] are the exchange rate constants between plasma and the extracellular space, k_3 [1/min] and k_4 [1/min] describe the transport in and out of the cell, k_5 [1/min] and k_6 [1/min] phosphorylation and dephosphorylation.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - (k_4 + k_5) C_2(t) + k_6 C_3(t)$$

$$\frac{dC_3(t)}{dt} = k_5 C_3(t) - k_6 C_3(t)$$

$$C_{Model}(t) = (1 - vB)\left[C_1(t) + C_2(t) + C_3(t)\right] + vB\, C_B(t)$$

with input curve $C_p(t)$.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t) + C_3(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 6 fitable parameters **vB**, **K1**, **k2**, **k3**, **k4**, **k5**, **k6**. Usually, **vB** is fixed at a physiologic value of 3-5%, and k_6 is fixed: **k6**=0. The influx **Ki** is given by

$$K_i = \frac{K_1 k_3 k_5}{k_2 k_4 + k_2 k_5 + k_3 k_5}$$

Reference

1. Bertoldo A, Peltoniemi P, Oikonen V, Knuuti J, Nuutila P, Cobelli C: Kinetic modeling of [18F] FDG in skeletal muscle by PET: a four-compartment five-rate-constant model. American journal of physiology Endocrinology and metabolism 2001;281(3):E524-536. PDF

6.1.21 3-Tissue Compartments with Metabolites

If a labeled metabolite of the tracer enters tissue, the additional signal has to be accounted for in the model. The current model introduced by Fujita et al. [1] includes a second input curve $C_M(t)$ of a metabolite entering tissue and undergoing non-specific binding.

C_1 represents the non-displaceable compartment of the authentic ligand, C_2 the specific binding of interest, and C_3 metabolized ligand in tissue.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_{1p} C_P(t) - (k_{2p} + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_3(t)}{dt} = K_{1m} C_M(t) - k_{2m} C_3(t)$$

with the input curves of authentic ligand and metabolite, $C_p(t)$ and $C_M(t)$, respectively. The input curve loading menu shows two corresponding entries as soon as the model is selected.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t) + C_3(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes the 7 fitable parameters **vB**, **K1p**, **k2p**, **k3**, **k4**, **K1m**, **k2m**. Due to the high number of parameters reliable fitting is difficult. There are two other model variants which support coupled fitting by using distribution volumes as fit parameters.

Models with Alternative Fit Parameters

There are two alternative models available which have the same structure but use some parameter ratios as fit parameters. The advantage is that these ratios might be candidates as common parameters among regions in a coupled fit, or might be fixed at known values.

Reference

1. Fujita M, Seibyl JP, Verhoeff NP, Ichise M, Baldwin RM, Zoghbi SS, Burger C, Staley JK, Rajeevan N, Charney DS et al: Kinetic and equilibrium analyses of [(123)I]epidepride binding to striatal and extrastriatal dopamine D(2) receptors. Synapse 1999, 34(4):290-304.

6.1.22 3-Tissue Compartments with Metabolites, K1/k2

If a labeled metabolite of the tracer enters tissue, the additional signal has to be accounted for in the model. The current model introduced by Fujita et al. [1] includes a second input curve $C_M(t)$ of a metabolite entering tissue and undergoing non-specific binding. C_1 represents the non-displaceable compartment of the authentic ligand, C_2 the specific binding of interest, and C_3 metabolized ligand in tissue.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_{1p} C_P(t) - (k_{2p} + k_3) C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_3(t)}{dt} = K_{1m} C_M(t) - k_{2m} C_3(t)$$

with the input curves of authentic ligand and metabolite, $C_p(t)$ and $C_M(t)$, respectively. The input curve loading menu shows two corresponding entries as soon as the model is selected.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t) + C_3(t)) + vB \, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using K_1/k_2

The **3-Tissue Compartments with Metabolites, K1/k2** model variant uses the parameter ratios **K1p/k2p**, **K1m/k2m** and **K1p/K1m**, as fitting parameters instead of k_{2p}, K_{1m} and k_{2m}. The advantage of this formulation is that the ratios may be fixed at known or assumed values, or estimated in a coupled fit. The other four fitting parameters **vB**, **K1p**, **k3**, and **k4** are the same as for the **3-Tissue Compartments with Metabolites** model.

Reference

1. Fujita M, Seibyl JP, Verhoeff NP, Ichise M, Baldwin RM, Zoghbi SS, Burger C, Staley JK, Rajeevan N, Charney DS et al: Kinetic and equilibrium analyses of [(123)I]epidepride binding to striatal and extrastriatal dopamine D(2) receptors. Synapse 1999, 34(4):290-304.

6.1.23 3-Tissue Compartments with Metabolites, K1/k2, Vs

If a labeled metabolite of the tracer enters tissue, the additional signal has to be accounted for in the model. The current model introduced by Fujita et al. [1] includes a second input curve $C_M(t)$ of a metabolite entering tissue and undergoing non-specific binding. C_1 represents the non-

displaceable compartment of the authentic ligand, C_2 the specific binding of interest, and C_3 metabolized ligand in tissue.

Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_{1p}C_P(t) - (k_{2p} + k_3)\,C_1(t) + k_4\,C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3\,C_1(t) - k_4\,C_2(t)$$

$$\frac{dC_3(t)}{dt} = K_{1m}\,C_M(t) - k_{2m}\,C_3(t)$$

with the input curves of authentic ligand and metabolite, $C_p(t)$ and $C_M(t)$, respectively. The input curve loading menu shows two corresponding entries as soon as the model is selected.

Operational Model Curve

$$C_{Model}(t) = (1 - vB)\,(C_1(t) + C_2(t) + C_3(t)) + vB\,C_B(t)$$
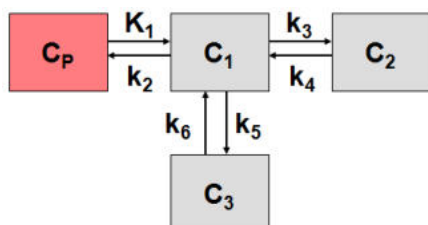
with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting using K_1/k_2 and VS

The **3-Tissue Compartments with Metabolites, K1/k2, Vs** model variant uses the parameter ratios **K1p/k2p**, **K1m/k2m**, **K1p/K1m**, and **Vs**=$K_{1p}/k_{2p}*k_3/k_4$ as fitting parameters instead of k_{2p}, K_{1m}, k_{2m}, and k_4. The advantage of this formulation is that the ratios may be fixed at known or assumed values, or estimated in a coupled fit. The other three fitting parameters **vB**, **K1p** and **k3** are the same as for the **3-Tissue Compartments with Metabolites** model.

Reference

1. Fujita M, Seibyl JP, Verhoeff NP, Ichise M, Baldwin RM, Zoghbi SS, Burger C, Staley JK, Rajeevan N, Charney DS et al: Kinetic and equilibrium analyses of [(123)I]epidepride binding to striatal and extrastriatal dopamine D(2) receptors. Synapse 1999, 34(4):290-304.

6.1.24 4-Tissue Compartments with Metabolites, K1/k2

This is a general compartment model for ligands which have recirculating metabolites entering tissue and contributing to tissue activity. Tissue kinetics of both the authentic ligand (C_1 and C_2) as well as the metabolites (C_3 and C_4) are described by a 2-tissue compartment model, with a transfer k_{trans} constant linking the two exchangeable compartments which represents metabolites generated in tissue.
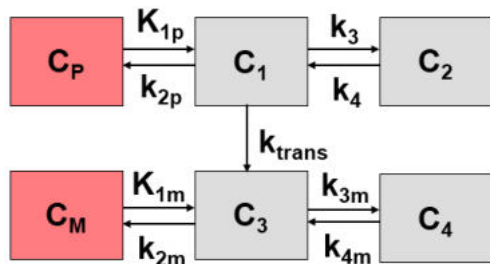
Differential Equation of the Mass Balance

$$\frac{dC_1(t)}{dt} = K_{1p}C_P(t) - (k_{2p} + k_3 + k_{trans})C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

$$\frac{dC_3(t)}{dt} = K_{1m}C_M(t) - (k_{2m} + k_{3m})C_3(t) + k_{trans}C_1(t) + k_{4m}C_4(t)$$

$$\frac{dC_4(t)}{dt} = k_{3m}C_3(t) - k_{4m}C_4(t)$$

Two input curves are required: the authentic ligand in plasma $C_p(t)$, and the metabolites exchanging with tissue $C_M(t)$. The input curve loading menu shows two corresponding entries as soon as the model is selected.

Operational Model Curve
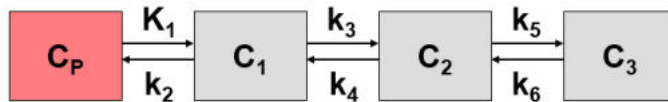
$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t) + C_3(t) + C_4(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of tracer in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes more parameters than can be reliably fitted at once. Therefore it has been implemented with **K1/k2** and **K1m/k2m** as fitting parameters to allow fixing the distribution volume of the exchangeable compartment, or to use them as common parameters in a coupled fit.

6.1.25 Flumazenil Triple-injection Model

This model corresponds to a triple-injection protocol developed by Delforge et al. [1] for [11C] flumazenil PET. The setup includes three injections of labeled and/or unlabeled ligand during a single acquisition. The model is based on a 2-tissue compartment structure and accounts for the saturation of the benzodiazepine receptor. The uptake and binding of both labeled and unlabeled ligand is modeled by two parallel compartment models linked by common model parameters.
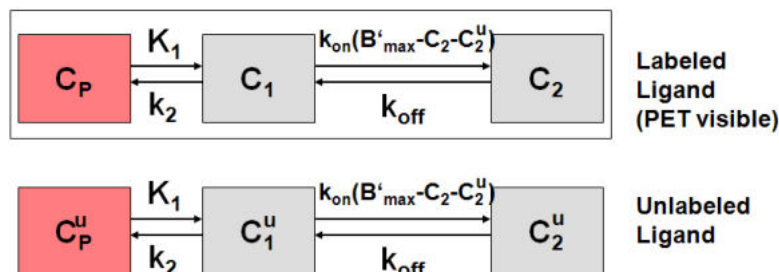
Differential Equation of the Mass Balance

They are linked by common model parameters and the system of differential equations

$$\frac{dC_1(t)}{dt} = k_1 C_P(t) - k_2 C_1(t) - \frac{k_{on}}{V_R} C_1(t)\left[B_{max} - C_2(t) - C^u_2(t)\right] + k_{off} C_2(t)$$

$$\frac{dC_2(t)}{dt} = \frac{k_{on}}{V_R} C_1(t)\left[B_{max} - C_2(t) - C^u_2(t)\right] - k_{off} C_2(t)$$

$$\frac{dC^u_1(t)}{dt} = k_1 C^u_P(t) - k_2 C^u_1(t) - \frac{k_{on}}{V_R} C^u_1(t)\left[B_{max} - C_2(t) - C^u_2(t)\right] + k_{off} C_2^u(t)$$

$$\frac{dC^u_2(t)}{dt} = \frac{k_{on}}{V_R} C^u_1(t)\left[B_{max} - C_2(t) - C^u_2(t)\right] - k_{off} C^u_2(t)$$

Note that only the labeled ligand can be measured, both in PET and in the blood samples. Therefore the input curve of unlabeled ligand $C^u_p(t)$ must be derived from the input curves of labeled ligand $C_p(t)$. This task is complicated by the fact of metabolite build-up in plasma which must be corrected for. With T_1, T_2 and T_3 denoting the time of the three injections, the input curve $C_p(t)$ of hot (labeled) tracer is calculated from the total plasma activity $C_{plasma}(t)$ as follows:

$$C_P(t) = \begin{cases} C_{Plasma}\left(A_1 e^{B_1(t-T_1)} + A_2 e^{B_2(t-T_1)}\right) & T_1 < t < T_3 \quad \text{decay since 1}^{st}\text{ injection} \\ C_{Plasma}\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \quad \text{decay since 3}^{rd}\text{ injection} \end{cases}$$

This metabolite correction is implemented as the input curve model **Multiinjection, HOT**.

The input curve $C^u_p(t)$ of cold (unlabeled) tracer is derived from $C_p(t)$ by the expression

$$C^u_P(t) = \begin{cases} Dose_2 / Dose_1\, C_P(t - T_2) & T_2 < t < T_3 \\ Dose_3{}^{Cold} / Dose_3{}^{Hot}\, C_P(t - T_3) + C^u_P(T_3)\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \end{cases}$$

which is implemented as the input curve model **Multiinjection, COLD**.

Operational Model Curve

Since PET only measures the radioactively labeled compounds the operational equation is given by

$$C_{Model}(t) = (1 - vB)(C_1(t) + C_2(t)) + vB\, C_B(t)$$

with the concentration $C_B(t)$ of labeled compounds in whole blood, and the blood volume fraction v_B.

Parameter Fitting

The model includes six parameters **vB**, **K1**, **k2**, **Kon/VR**, **koff**, **Bmax** which are normally not possible to fit at once. However, the complex injection protocol results in more complex tissue TACs than with the usual single-injection protocols. As a consequence, the model has proven to result in reliable estimates of B_{max}.

Reference

1. Delforge J, Pappata S, Millet P, Samson Y, Bendriem B, Jobert A, Crouzel C, Syrota A: Quantification of benzodiazepine receptors in human brain using PET, [11C]flumazenil, and a single-experiment protocol. J Cereb Blood Flow Metab 1995, 15(2):284-300. DOI

Acknowledgement

6.1.26 Water PET Model with Flow and Dispersion

This model implements the 1-tissue compartment model for $H_2^{15}O$ water PET studies developed by E. Meyer [1].
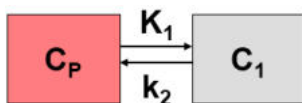
Operational Model Curve

It is assumed that at by the arrival in tissue the true input curve $C_p(t)$ has been dispersed. This dispersion is modeled by convolving $C_p(t)$ with an exponential kernel

$$d(t) = \frac{1}{\tau} e^{-t/\tau}$$

whereby the parameter τ is called *Dispersion*. Incorporating the convolution into the 1-tissue compartment model and solving it using the Laplace transform yields the following analytic formula for the tissue concentration

$$C_1(t) = \tau K_1 C_P(t) + (1 - \tau k_2) K_1 e^{-k_2 t} \int_0^t C_P(\tau) e^{k_2 \tau} d\tau$$

K_1 represents flow, and k_2 flow divided by the partition coefficient p.

The operational equation is given by

$$C_{Model}(t) = (1 - vB) C_1(t) + vB\, C_B(t)$$

Note that in this particular case there is no difference between the plasma and blood concentrations $C_p(t)$ and $C_B(t)$ because water is a freely diffusible tracer.

Parameter Fitting

The tissue model includes four fitable parameters **vB**, **K1**, **k2**, (Flow/Part.Coeff), τ (Dispersion). Per default, however, v_B is fixed at **vB**=0 as in the original model. For water studies with the blood activity sampled in a peripheral artery, the resulting input curve is delayed respect to the arrival in tissue. In this case, the model should be fitted using the **Fit region and blood delay** button.

Implementation Note

Unlike the standard compartment models in PKIN the model curve of the operational equation is not calculated by integrating a set of differential equations, but rather using the analytical solution given above. The convolution integral is approximated by summing rectangles of 0.1sec in length, assuming that the acquisition time of dynamic water studies is short.

Reference

1. Meyer E: Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the H215O autoradiographic method and dynamic PET. J Nucl Med 1989, 30(6):1069-1078. PDF

6.2   Compartment Models for Cardiac PET

Model Name	Description
Card. NH3 (de Grado) [140]	1-Tissue compartment model with two spillover terms. Has been developed for cardiac NH_3-PET studies with bolus administration. The left

	ventricle input curve is linearly corrected for metabolites.
Card. NH3 (UCLA, 2 Parameters) [141]	2-Tissue compartment model with only 2 fitted parameters. Has been developed for cardiac NH$_3$-PET studies with bolus administration. It only uses the first 2 minutes of the data as there is not metabolite correction included.
Card. NH3 (2 Compartments) [143]	2-Tissue compartment model with metabolic trapping. Has been developed for cardiac NH$_3$-PET studies with bolus administration. Also implements metabolite correction.
Card. Rb-82 (1 Compartment) [145]	1-compartment model for the quantification of myocardial perfusion with Rubidium-82 PET data.
Card. Rb-82 (2 Compartment) [146]	Two-compartment model for the quantification of myocardial perfusion with Rubidium-82 PET data.
Card. H2O (Tissue fraction) [147]	1-Tissue compartment model with two spillover terms. Has been developed for cardiac H$_2$^{15}O- PET studies with bolus administration.
Card. H2O (Geometrical corr.)	As above, but with geometrical spillover correction.
Card. Acetate (1 Compartment) [148]	1-compartment model for the quantification of myocardial perfusion with ^{11}C Acetate PET data.

Assumptions of the Cardiac Models
- The cardiac models usually apply a geometrical spillover with two correction terms: correction for signal from the left and right ventricular cavity.
- For calculating the myocardial perfusion per g tissue a density of 1.04 g/ml for myocardial tissue is applied.
- Usually the PET signal from the left ventricle or the atrium is used as a measure of the tracer activity in blood. Depending on the tracer, corrections are applied to this blood curve for calculation the concentration of parent tracer with is required as the input curve of the models.

Exceptions to these rules are specified in the description of the individual models.

6.2.1   Cardiac Perfusion from Ammonia PET

There are three model variants available for the quantification of myocardial blood flow from ^{13}NH$_3$ ammonia bolus PET data, the 1-tissue compartment model and the 2-tissue compartment model with metabolic trapping. The 1-tissue model is preferably used with the first 2-4 minutes of a dynamic measurement, while the 2-tissue model is also adequate for longer durations. This may compensate to some extent the increased vulnerability to identifiability problems due to the higher number of fit parameters in the 2-tissue model.

6.2.1.1   Card. NH3 (de Grado)

The **Card. NH3(De Grado)** model has been developed by DeGrado et al. [1] for cardiac PET studies using ^{13}NH$_3$ ammonia bolus injection. It is based on a 1-tissue compartment model with plasma activity $C_P(t)$ and total uptake in myocardium $C_{myo}(t)$.
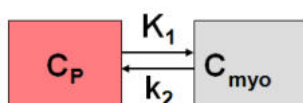
Operational Model Curve

The plasma activity is calculated from the total activity in the left ventricular cavity $C_{lv}(t)$ by a linear metabolite correction with factor mCorr

$$C_P(t) \;=\; (1 - mCorr * t)C_{lv}(t)$$

A value of mCorr=0.077 [1/min] has been found in humans [1]. The resulting differential equation for myocardial uptake is

$$\frac{dC_{myo}(t)}{dt} \;=\; K_1 C_P(t) - k_2 C_{myo}(t)$$

where K_1 equals myocardial blood flow F. The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) \;=\; (1 - V_{LV} - V_{RV})\,C_{myo}(t) + V_{RV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricle $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricle $C_{RV}(t)$.

DeGrado et al. recommend to only use the first 4 minutes of data after injection of the tracer to reduce the effects of metabolite buildup and washout.

Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.
- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.
- The **valid** flag for all data samples after 4 minutes is set to false, and they are consequently not considered in the fit.

Parameter Fitting

The model includes the 4 fitable parameters **F**, **vRV**, **vLV** and **k2**. Please inspect the **%SE** standard error to get information about the reliability of the parameter estimates.

Reference

1. DeGrado TR, Hanson MW, Turkington TG, Delong DM, Brezinski DA, Vallee JP, Hedlund LW, Zhang J, Cobb F, Sullivan MJ et al: Estimation of myocardial blood flow for longitudinal studies with 13N-labeled ammonia and positron emission tomography. J Nucl Cardiol 1996, 3(6 Pt 1):494-507.

6.2.1.2   Card. NH3 (UCLA, 2 Parameters)

This model implements a 2-tissue compartment model with only two fitted tissue rate constants. It was developed by Choi et al. for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection and was called the *Modified Two-Parameter Model*, [1] eq (5).
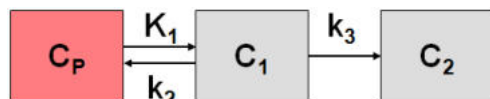
Operational Model Curve

The system of compartmental differential equations for this compartment structure is given by

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

with K_1 corresponding to myocardial blood flow F. The k_3 rate constant corresponding to glutamine formation was converted into a K_1-dependent value by the relation

$$k_3 = K_1\left(1.65\, e^{1.25/K_1} - 1\right)$$

Similarly, the k_2 rate constant of ammonia washout was converted into a K_1-dependent value by

$$k_2 = K_1 / V_{ND}$$

with the V_{ND} representing the distribution volume of ammonia in the C_1 compartment which was assumed to be constant (V_{ND}=0.8).

In contrast to Choi's method, the model incorporates not only a spillover from the left ventricle, but for septal regions also from the right ventricle. The operational equation is then given by

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})(C_1(t) + C_2(t)) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricle $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricle $C_{RV}(t)$.

Because the model does not include a metabolite correction, only the samples within 2 minutes after injection should be used for the fit [1].

Implementation Notes:

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve.
- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.
- The **valid** flag for all data samples after 2 minutes is set to false, and they are consequently not considered in the fit.

Parameter Fitting

The model includes the three fitable parameters **F**, **vLV**, **vRV**. Please inspect the **%SE** standard error to get information about the reliability of their estimates. The input parameters **Vnd** (0.8), **EF scale** (1.65) and **EF Exp** (1.25) are related to the conversion of k_2 and k_3 as described above and can be adjusted if needed.

Reference

1. Choi Y, Huang SC, Hawkins RA, Kim JY, Kim BT, Hoh CK, Chen K, Phelps ME, Schelbert HR: Quantification of myocardial blood flow using 13N-ammonia and PET: comparison of tracer models. J Nucl Med 1999, 40(6):1045-1055. PDF

6.2.1.3 Card. NH3 (2 Compartments)

The **Card NH3 (2-Tissue)** model developed by Hutchins et al. [1] is an implementation of the irreversible 2-tissue-compartment model for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection. The compartment model has the following structure

where C_1 is free tracer in tissue, and C_2 is metabolically trapped tracer in the form of ^{13}N glutamine. Because ammonia is considered in this model as freely diffusible across the capillary wall, the unidirectional uptake parameter K_1 equals the myocardial perfusion.

Operational Model Curve

The system of differential equations is

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

To allow the fitting of data over an extended period, the model includes the exponential metabolite correction described by van den Hoff et al. [2]

$$C_P(t) = \begin{cases} C_{LV}(t) & t \le t_0 \\ e^{-\ln 2(t-t_0)/T_{1/2}} C_{LV}(t) & t > t_0 \end{cases}$$

with a delay t_0=0.48 min and half-time $T_{1/2}$=6.69 min. $C_{LV}(t)$ is the total tracer concentration measured in the left ventricular cavity, including metabolites.

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})(C_1(t) + C_2(t)) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricle $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricle $C_{RV}(t)$.

Implementation Notes:

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.

- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

- The **valid** flag for all data samples after 2 minutes is set to false, and they are consequently not considered in the fit.

Parameter Fitting

The model includes the five fitable parameters **F**, **vLV**, **vRV**, **k2**, **k3**. Please inspect the **%SE** standard error to get information about the reliability of their estimates. The input parameters **MC**

T0 (0.48) and **MC T12** (6.69) are related to the metabolite correction as described above and can be adjusted if needed.

Alternate Model Card NH3 (2-Tissue, K_1/k_2)

Due to the increased number of fit parameters it has been found, that the **Card NH3 (2-Tissue)** may suffer from identifiability problems. Therefore, the variant **Card NH3 (2-Tissue, K1/k2)** has been developed using the parameter K_1/k_2 (distribution volume of the first compartment) as a fit parameter instead of k_2. In this configuration physiological restrictions can be imposed on K_1/k_2, or K_1/k_2 can be used as a common parameter in a coupled fit 41.

References

1. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE: Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990, 15(5):1032-1042.

2. van den Hoff J, Burchert W, Borner AR, Fricke H, Kuhnel G, Meyer GJ, Otto D, Weckesser E, Wolpers HG, Knapp WH: [1-(11)C]Acetate as a quantitative perfusion tracer in myocardial PET. J Nucl Med 2001, 42(8):1174-1182. PDF

6.2.1.4 Card. NH3 (2 Compartments, K1/k2)

The **Card NH3 (2-Tissue)** model developed by Hutchins et al. [1] is an implementation of the irreversible 2-tissue-compartment model for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection. The compartment model has the following structure

where C_1 is free tracer in tissue, and C_2 is metabolically trapped tracer in the form of ^{13}N glutamine. Because ammonia is considered in this model as freely diffusible across the capillary wall, the unidirectional uptake parameter K_1 equals the myocardial perfusion.

Operational Model Curve

The system of differential equations is

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$
$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

To allow the fitting of data over an extended period, the model includes the exponential metabolite correction described by van den Hoff et al. [2]

$$C_P(t) = \begin{cases} C_{LV}(t) & t \le t_0 \\ e^{-\ln 2(t-t_0)/T_{1/2}} C_{LV}(t) & t > t_0 \end{cases}$$

with a delay t_0=0.48 min and half-time $T_{1/2}$=6.69 min. $C_{LV}(t)$ is the total tracer concentration measured in the left ventricular cavity, including metabolites.

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})(C_1(t) + C_2(t)) + V_{LV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricle $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricle $C_{RV}(t)$.

Implementation Notes:

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.

- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

- The **valid** flag for all data samples after 2 minutes is set to false, and they are consequently not considered in the fit.

Parameter Fitting

The model includes the five fitable parameters **F**, **vLV**, **vRV**, **K1/k2**, **k3**. The parameter **K1/k2** (distribution volume of the first compartment) is used as a fit parameter instead of k_2. In this configuration physiological restrictions can be imposed on K_1/k_2 , or K_1/k_2 can be used as a common parameter in a coupled fit $\boxed{41}$. **k2** is derived from the estimated **F** ($=K_1$) and **K1/k2**. Please inspect the **%SE** standard error to get information about the reliability of their estimates.

The input parameters **MC T0** (0.48) and **MC T12** (6.69) are related to the metabolite correction as described above and can be adjusted if needed.

References

1. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE: Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990, 15(5):1032-1042.

2. van den Hoff J, Burchert W, Borner AR, Fricke H, Kuhnel G, Meyer GJ, Otto D, Weckesser E, Wolpers HG, Knapp WH: [1-(11C)]Acetate as a quantitative perfusion tracer in myocardial PET. J Nucl Med 2001, 42(8):1174-1182. PDF

6.2.2 Cardiac Perfusion from Rubidium-82 PET

Two kinetic models are available for the quantification of myocardial perfusion from ^{82}Rb bolus PET data.

1. A 1-tissue compartment model with geometrical spillover correction and correction for flow-dependent extraction.

2. A 2-tissue compartment model with recovery and spillover correction.

6.2.2.1 Card. Rb-82 (1 Compartment)

The **Card. Rb82(1 Compartment)** model has been developed by Lortie et al. [1] for cardiac PET studies using ^{82}Rb bolus injection. It is based on a 1-tissue compartment model with plasma activity $C_P(t)$ and total uptake in myocardium $C_{myo}(t)$.

Operational Model Curve

The differential equation is given by

$$\frac{dC_{myo}(t)}{dt} = K_1 C_P(t) - k_2 C_{myo}(t)$$

The model uses the activity in the left ventricular cavity $C_{lv}(t)$ is used as the input curve ($C_P(t)$ =$C_{LV}(t)$). Rb is known to have a flow-dependent extraction fraction, so that K_1, which is the product of flow F times extraction fraction E, is described by the expression

$$K_1 = F\,E = F\,(1 - Ae^{-B/F})$$

This expression is inserted for K_1 into the differential equation, so that F becomes a fit parameter, and K_1 is derived from it. The values of the extraction parameters reported by Lortie et al. [1] are

A = 0.77
B = 0.63 [ml/min/g]

They can be entered as input parameters into the model for changing the form of the extraction function. The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})\,C_{myo}(t) + V_{RV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricular cavity $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricular cavity $C_{RV}(t)$

Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve.
- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

Parameter Fitting

The model includes the 4 fitable parameters **F**, **vRV**, **vLV** and **k2**. Please inspect the %SE standard error to get information about the reliability of the parameter estimates. The scale factor A (**EF scale**) and the exponent B (**EF exp**) of the extraction function can be entered as input parameters.

Reference

1. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA: Quantification of myocardial blood flow with 82Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging 2007, 34(11):1765-1774.

6.2.2.2   Card. Rb-82 (2 Compartments)

The **Card. Rb-82 (2 Compartments)** model has been implemented according to the method described and evaluated by Herrero et al [1]. The model is based on the following compartment structure to describe the kinetics of rubidium in the myocardium:
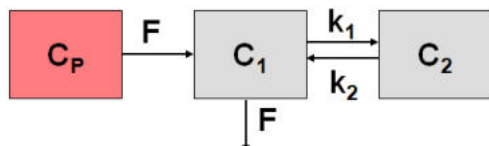
where $C_1(t)$ represents the fast exchangeable compartment (vascular and interstitial spaces), and $C_2(t)$ the slow exchangeable compartment (intracellular space), myocardium flow F, and rate constants k_1 and k_2.

Operational Model Curve

The differential equations for the activity concentrations in the different compartments are given by

$$\frac{dC_1(t)}{dt} = F(C_P(t) - C_1(t)) - k_1 C_1(t) + k_2 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_1 C_1(t) - k_2 C_2(t)$$

The model uses the activity in the left ventricular cavity $C_{LV}(t)$ is used as the input curve ($C_P(t) = C_{LV}(t)$). The operational equation which is fitted to the measured data is

$$C_{Model} = F_{MM} (C_1(t) + C_2(t)) + F_{BM} C_{LV}(t)$$

where F_{MM} denotes the tissue recovery coefficient and F_{BM} the blood to myocardium spillover fraction.

Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the left ventricle curve must be loaded as the **Plasma activity** curve. The right ventricle curve is not used.

Parameter Fitting

The model encompasses 5 fitable parameters. However, in practice it is impossible to estimate so many parameters from a time-activity curve with reasonable identifiability. Therefore, at least the the recovery coefficient **FMM** is usually fixed. The default from Herrero et al [1] is 0.65, but it depends on the image resolution and should be determined experimentally.

Reference

1. Herrero P, Markham J, Shelton ME, Bergmann SR: Implementation and evaluation of a two-compartment model for quantification of myocardial perfusion with rubidium-82 and positron emission tomography. Circulation research 1992, 70(3):496-507. DOI

6.2.3 Cardiac Perfusion from Water PET

The **Card. H2O (Tissue fraction)** model has was developed by Hermannsen et al. [1] for cardiac PET studies using $H_2^{15}O$ water bolus injection. The distribution of the freely diffusible inert tracer $H_2^{15}O$ in myocardium can be described by a 1-tissue compartment model with myocardial blood flow F and the partition coefficient of water p, which is defined as (ml water/ml tissue)/(ml water/ml blood).

Operational Model Curve

The differential equation for the tracer concentration in myocardium is

$$\frac{dC_{myo}(t)}{dt} = F C_P(t) - \frac{F}{p} C_{myo}(t)$$

In practice, the left ventricular time-activity curve is used as the input curve $C_P(t)$.

The model curve incorporates two spill-over terms from blood in the left and the right ventriclar cavities which are relatively displaced in time. So the operational equation which is fitted to the measured data is

$$C_{Model}(t) = TF\, C_{myo}(t) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where TF = tissue fraction, V_{LV} = spill-over fraction from the left ventricle, V_{RV} = spill-over fraction from the right ventricle.

Implementation

As opposed to most models in PKIN a tissue fraction is used for calculating the model curve rather than a strict geometrical correction for compliance with the original model. When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve.
- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

Parameter Fitting

The model encompasses the 5 fitable parameters **F**, **TF**, **vLV**, **vRV** and **p**. However, in practice it is impossible to estimate so many parameters from a time-activity curve with reasonable identifiability. The partition coefficient is therefore fixed per default at a value of 0.96 [1], and the spillover fraction from right ventricular blood vRV is only fitted for septal tissue TACs.

Reference

1. Hermansen F, Rosen SD, Fath-Ordoubadi F, Kooner JS, Clark JC, Camici PG, Lammertsma AA: Measurement of myocardial blood flow with oxygen-15 labelled water: comparison of different administration protocols. Eur J Nucl Med 1998, 25(7):751-759. PDF

6.2.4 Cardiac Perfusion from Acetate PET

Van den Hoff et al. [1] have investigated and validated ^{11}C-acetate as a flow tracer. This methodology is implemented as the **Card Acetate (1 Compartment)** model. It employs a single tissue compartment model
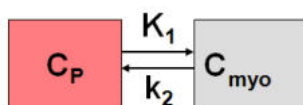
with tracer exchange between arterial plasma $C_P(t)$ and myocardial tissue $C_{myo}(t)$.

Operational Model Curve

The differential equation $C_{myo}(t)$ is given by

$$\frac{dC_{myo}(t)}{dt} = K_1\, C_P(t) - k_2\, C_{myo}(t) = EF\, C_P(t) - k_2\, C_{myo}(t)$$

K_1 is the product of flow F and extraction E

$$K_1 = E \cdot F$$

For acetate, the extraction is flow dependent [1]

$$E(F) = 1 - 0.64e^{-1.2/F}$$

Furthermore a metabolite correction is necessary to derive the plasma activity from whole blood measured in the left cavity [1]

$$C_P = 0.91e^{-\ln 2(t/T_{1/2})}C_{LV}(t)$$

with $T_{1/2}$=5.3 min. Including these relations into the differential equation yields

$$\frac{dC_{myo}(t)}{dt} = F(1 - 0.64e^{-1.2/F})0.91e^{-\ln 2(t/T_{1/2})}C_{LV}(t) - k_2\, C_{myo}(t)$$

which is non-linear in F. The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})\,C_{myo}(t) + V_{RV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricular cavity $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricular cavity $C_{RV}(t)$

Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.

- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

Parameter Fitting

The model includes the 4 fitable parameters **F**, **k2**, **vLV**, **vRV**. Please inspect the **%SE** standard error to get information about the reliability of the parameter estimates. The parameters for the correction of the flow-dependent extraction (**EF scale**, **EF exp**) and the metabolites (**MC scale**, **MC T12**) are initialized with the published values [1], but can be edited if needed. The **K1** parameter of the 1-tissue compartment model equivalent to the EF product is provided as s macro parameter.

Reference

1. van den Hoff J, Burchert W, Borner AR, Fricke H, Kuhnel G, Meyer GJ, Otto D, Weckesser E, Wolpers HG, Knapp WH: [1-(11)C]Acetate as a quantitative perfusion tracer in myocardial PET. J Nucl Med 2001, 42(8):1174-1182. PDF

6.3   Compartment Models for Cardiac SPECT

Due to recent improvements of SPECT cameras regarding sensitivity and time resolution, similar protocols as for cardiac perfusion PET have been developed and tested. To date, however, there is no consensus regarding the analysis of such data. In order for researchers to experiment with such data, PMOD offers one of the recently published methods, which fits well into the existing framework.

6.3.1 Cardiac Perfusion from 99mTc Tetrofosmin SPECT

The **Card. 99mTc Tetrofosmin (Shrestha)** model has been developed by Shrestha et al. [1] for cardiac SPECT studies using [99mTc] Tetrofosmin bolus injection. It is based on a 1-tissue compartment model with plasma activity $C_P(t)$ and total uptake in myocardium $C_{myo}(t)$.

Operational Model Curve

The differential equation is given by

$$\frac{dC_{myo}(t)}{dt} = K_1 C_P(t) - k_2 C_{myo}(t)$$

The model uses the activity in the left ventricular cavity $C_{lv}(t)$ is used as the input curve ($C_P(t)$ = $C_{LV}(t)$). Rb is known to have a flow-dependent extraction fraction, so that K_1, which is the product of flow F times extraction fraction E, is described by the expression

$$K_1 = FE = F(1 - Ae^{-B/F})$$

This expression is inserted for K_1 into the differential equation, so that F becomes a fit parameter, and K_1 is derived from it. The values of the extraction parameters reported by Shrestha et al. [1] are

A = 0.91
B = 0.34 [ml/min/g]

They can be entered as input parameters into the model for changing the form of the extraction function. The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})C_{myo}(t) + V_{RV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

where
V_{LV} = spill-over fraction of the blood activity in the left ventricular cavity $C_{LV}(t)$,
V_{RV} = spill-over fraction of the blood activity in the right ventricular cavity $C_{RV}(t)$

Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- The left ventricle curve must be loaded as the **Plasma activity** curve.
- The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- The spill-over fraction from the right ventricle V_{RV} is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

Parameter Fitting

The model includes the 4 fitable parameters **F**, **vRV**, **vLV** and **k2**. Please inspect the %SE standard error to get information about the reliability of the parameter estimates. If necessary, the scale factor A (**EF scale**) and the exponent B (**EF exp**) of the extraction function can be interactively edited.

Reference

π.pmod

1. Shrestha U, Sciammarella M, Alhassen F, Yeghiazarians Y, Ellin J, Verdin E, Boyle A, Seo Y, Botvinick EH, Gullberg GT: Measurement of absolute myocardial blood flow in humans using dynamic cardiac SPECT and (99m)Tc-tetrofosmin: Method and validation. J Nucl Cardiol 2017, 24(1):268-277.

6.4   Reference Tissue Models

PKIN features the following list of reference models which are mostly used for the analysis of receptor ligand studies:

Model Name	Description
4 Parameter Reference Tissue Model [152]	4 Parameter Reference Tissue Model by Lammertsma et al.
SRTM [153]	Simplified Reference Tissue Model by Lammertsma and Hume
SRTM2 [154]	Modification of Simplified Reference Tissue Model by Wu and Carson to reduce BP bias induced by noise
MRTM0 [158]	Original Multilinear Reference Tissue Model by Ichise et al.
MRTM [160]	Multilinear Reference Tissue Model by Ichise et al modified to reduce bias induced by noise
MRTM2 [161]	Multilinear Reference Tissue Model by Ichise et al modified to reduce bias and variability induced by noise
Logan Non-Invasive [157]	Reference tissue method which is based on an average k_2
2 Tissue Reference Model [163]	Watabe's reference tissue model with a 2-tissue compartment model in the reference region
MP4A RLS (Nagatsuka) [165]	Multi-linear Reference Tissue Model for [11C]-MP4A (RLS)

6.4.1   Coupled fitting for Determination of k2' in Reference Tissue Models

Some of the reference methods require an a priori average value of k_2', while other methods such as the MRTM or the SRTM reference methods estimate k_2' together with the other parameters in every pixel.

Averaging k2' from Separate Regional Fits

In response to a request from a PMOD user Dr. Ichise recommended the following approach for calculating k_2':

1. k_2' is the tissue clearance rate from the reference region, e.g., cerebellum. This reference tissue is always a region (ROI), not a voxel for both ROI based PKIN or PXMOD parametric imaging. If you define a reference region, there should be only one correct k_2' value for that particular subject (scan).

2. Logan in her original formulation of her reference tissue model suggested to determine k_2' by using arterial data for a group of subjects and use this mean k_2'.

3. However, we showed that this k_2' can be estimated for each individual without arterial data using MRTM or SRTM (three parameter estimation, one of the three parameters is k_2').

4. I prefer to use k_2' estimated this way for each subject for the subsequent MRTM2 or SRTM2. This would be more accurate than the mean k_2' estimated for a group of subjects as above.

5. Now the accuracy of k_2' estimation depends on the following (see [52]): A) noise in the PET data, B) the magnitude of k_2' and C) the ratio of k_2'/k_2 or k_2/k_2' determined by MRTM or SRTM.

6. The bias and variability of k_2' estimation by MRTM is less as k_2' is larger and k_2'/k_2 or k_2/k_2' ratio is further away from unity. This ratio for fallypride using cerebellum and striatum should be greater than 3, I think. In that case, k_2' estimation from cerebellum and striatum (use ROIs) should be minimum (see figs in the paper).

7. Even using the ROIs, k_2' estimation is affected by noise and hence it is good to run MRTM a few times choosing ROIs with high BP_{ND} areas (say right striatum and left striatum) k_2'/k_2 ratio is further away from 1) and average the k_2' values. This averaging is within the subject and totally different from population average.

8. Please use the k_2' determined as above for estimation of BP_{ND} for the cortical regions. The k_2' estimated with cerebellum and cortical regions is not accurate because k_2'/k_2 is closer to unity.

9. One advantage of MRTM over SRTM: To use SRTM, both cerebellum and target must be 1 tissue (1T) kinetics (use of the SRTM for 2T will bias BP_{ND}). However, MRTM is good for tracers with 2T kinetics such as Fallypride. The only thing here is that you have to give a t* value.

Estimating k2' using a Fit with Regional Coupling

Alternatively, the a-priori knowledge that k_2' should always have the same value can be exploited using coupled fitting in PKIN with SRTM2 as described here 65. The k_2' value obtained in PKIN can then be used in PXMOD.

Maintaining of k2' when Switching Reference Tissue Models

Note that an estimated k_2' can be maintained when switching between reference tissue models by enabling Parameter Propagation 51. This allows for instance to keep k_2' estimated with SRTM2 when switching to the Logan reference tissue model.

6.4.2 Full Reference Tissue Model

Model Configuration and Assumptions

The **Full Reference Tissue** method (or *4 Parameter Reference Tissue Method*) of Lammertsma et al. is used for the analysis of studies with reversibly binding neuroreceptor tracers. A reference tissue devoid of receptors is required which can be modeled by a single-tissue compartment model. Tissues of interest which include the target receptor are modeled by a 2-tissue compartment model.
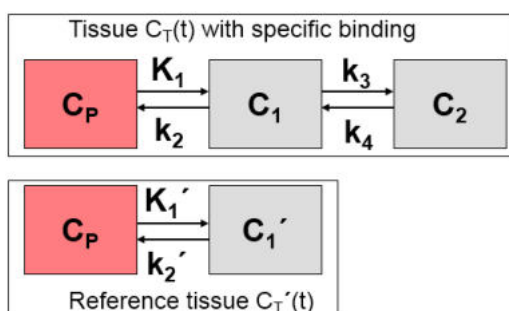
In the model equations C_T'(t) represents the tissue TAC from the reference region (k_3=0 in the 2-tissue compartment model), and C_T(t) the tissue TAC from a receptor-rich region (k_3>0). It is assumed that the distribution volume of the non-displaceable compartment is the same for tissues of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$. Furthermore the reference tissue should not affected by the pathology investigated under study.

Operational Model Curve

Defining the ratio of tracer delivery R_1 as K_1/K_1' and the binding potential BP_{ND} as k_3/k_4, the following operational equation can be derived for the measured tissue TAC in a receptor-rich region:

$$C_{Model}(t) \;=\; R_1 \left\{ C_T'(t) + a C_T'(t) \otimes e^{-ct} + b C_T'(t) \otimes e^{-dt} \right\}$$

The equation parameters and their relation to the model are given by:

$$a = (k_3 + k_4 - c)(c - r)/p$$
$$b = (d - k_3 - k_4)(d - r)/p$$
$$c = (s + p)/2$$
$$d = (s - p)/2$$
$$p = \sqrt{s^2 - q}$$
$$q = 4k_2 k_4$$
$$r = k_2 / R_1$$
$$s = k_2 + k_3 + k_4$$

For convolution with the exponentials, the reference tissue TAC $C_T'(t)$ is resampled on a regular grid, which can be specified by the **Resampling** parameter.

Parameter Fitting

The operational equation includes four unknowns: **R1**, **k2**, **k3**, and **BPnd** (after substitution of $BP_{ND}=k_3/k_4$), which can be fitted using nonlinear fitting techniques.

Reference

1. Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, Frackowiak RS: Comparison of methods for analysis of clinical [11C]raclopride studies. J Cereb Blood Flow Metab 1996, 16(1):42-52. **DOI**

6.4.3 Simplified Reference Tissue Model (SRTM)

Model Configuration and Assumptions

The **Simplified Reference Tissue Model** (SRTM) of Lammertsma and Hume [1] is used for the analysis of studies with reversibly binding neuroreceptor tracers. A reference tissue devoid of receptors is required which can be modeled by a single-tissue compartment model.

The assumptions of the model are:

1. The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

2. The kinetics in the receptor-rich tissue of interest is such that it is difficult to distinguish between the specific and the non-displaceable compartment; ie. the tissue TAC can be fitted by a 1-tissue compartment model with an uptake rate constant $k_{2a} = k_2/(1+BP_{ND})$. Note that this assumption may not be valid for all tracers, and in this case SRTM calculates biased BP_{ND} estimates.
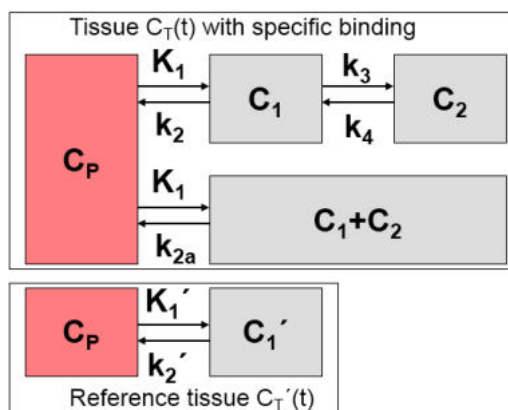
The model is a further development of the **4 Parameter Reference Tissue** method. It has been shown to be less dependent on the initial parameter values, more stable in the presence of noise, and provide more consistent estimates of relative tracer delivery R_1.

Operational Model Curve

Defining the ratio of tracer delivery R_1 as K_1/K_1' and the binding potential BP_{ND} as k_3/k_4, the following operational equation can be derived for the measured tissue TAC in a receptor-rich region:

$$C_{Model}(t) = R_1 C_T'(t) + \left[k_2 - R_1 k_2/(1 + BP_{ND}) \right] C_T'(t) \otimes e^{-k_2 t/(1 + BP_{ND})}$$

For convolution with the exponentials, the reference tissue TAC C'(t) is resampled on a regular grid, which can be specified by the **Resampling** parameter.

Parameter Fitting

The operational equation includes four unknowns: **R1**, **k2**, and **BPnd** , which can be fitted using nonlinear fitting techniques. **k2'**, the transfer of tracer from the reference tissue back to the plasma, is provided as a derived parameter, as well as **k2a**.

Note: The reference methods MRTM2 and SRTM2 require k_2' as an input parameter. The k_2' resulting from the SRTM method is a suitable estimate. Therefore, when switching in PKIN from the SRTM model to the SRTM2 or MRTM2, k_2' is automatically copied from SRTM, in case the **Model conversion** option in the **Extras** panel is enabled.

Reference

1. Lammertsma AA, Hume SP: Simplified reference tissue model for PET receptor studies. Neuroimage 1996, 4(3 Pt 1):153-158. **DOI**

6.4.4 Simplified Reference Tissue Model 2 (SRTM2)

Model Configuration and Assumptions

The **Simplified Reference Tissue Model 2** (SRTM2) was derived by Wu and Carson [1] from the **SRTM** 153 with the aim of improved parametric mapping. The model structure is the same
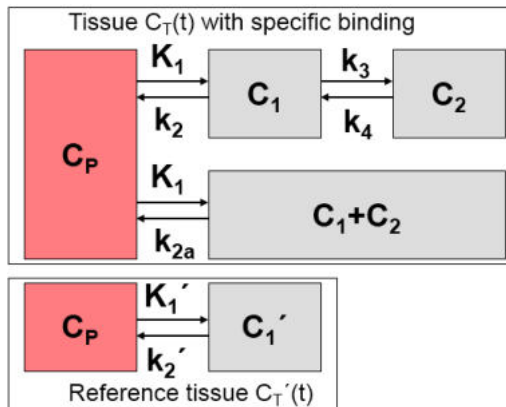
as well as the assumptions:

1. The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2 = K_1'/k_2'$.

2. The kinetics in the receptor-rich tissue of interest is such, that it is difficult to distinguish between the specific and the free/non-specific compartment; ie. the TAC can be fitted by a 1-tissue compartment model with an uptake rate constant $k_{2a} = k_2/(1+BP_{ND})$.

Operational Model Curve

The operational equation of the SRTM was re-written to allow for fixing of k_2'. This is relevant for parametric mapping because the model in each pixel TAC uses the same reference TAC and therefore should employ the same k_2'. Defining the ratio of tracer delivery R_1 as K_1/K_1' and the binding potential BP_{ND} as k_3/k_4, the following operational equation can be derived for the measured TAC in a receptor-rich region:

$$C_{Model}(t) = R_1 C_T'(t) + R_1\left[k'_2 - k_{2a}\right]C_T'(t) \otimes e^{-k_{2a}t}$$

The three unknowns R_1, k_2' and k_{2a} in this equation can be fitted using nonlinear regression techniques. The binding potential can then be calculated as

$$BP_{ND} = R_1 \frac{k'_2}{k_{2a}} - 1.0$$

For convolution with the exponentials, the reference tissue TAC $C_T'(t)$ is resampled on a regular grid, which can be specified by the **Resampling** parameter.

Parameter Fitting

The operational equation includes three unknowns: **R1**, **k2'**, and **k2a** which can be fitted using nonlinear fitting techniques. Note that **k2'**, the transfer of tracer from the reference tissue back to the plasma, can also be fitted. This can be employed by first estimating k_2' with a coupled fit and adequate TACs, and then fixing it for all regional fits as described **above** 151. Furthermore, fixing of k_2' allows studying the bias introduced by an inadequate k_2'.

> **Note:** As with the SRTM method, BP_{ND} estimates from SRTM2 tend to be biased if the 1-tissue compartment model assumption does not apply. The magnitude of the bias is even larger, most likely because the fixed k_2' can not compensate any more a part of the model inadequacy.

Reference

1. Wu Y, Carson RE: Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. J Cereb Blood Flow Metab 2002, 22(12):1440-1452. **DOI**

6.4.5   Linear Simplified Reference Tissue Model (LSRTM)

This model was developed by Alpert et al. [1] to extend the concept of activation studies for including measurements targeting neurotransmitters and specific receptor populations. It uses the fact that cognitive activation increases neuronal firing rate, hereby increasing the endogenous neurotransmitter level and altering the kinetics of specifically bound radioligands. The methodology uses a single PET injection. The scan starts with an acquisition of the subject at rest (baseline), followed by an acquisition with the subject performing a task (activation). The data (after motion correction of the lengthy scan) is analyzed modeling the change of the endogenous neurotransmitter level as an effect which occurs immediately after the task onset, and diminishes exponentially over time. The method has been applied to [11C]raclopride [1] and more recently to [18F]fallypride data [2,3].

Note: The model has been called LSSRM [1,2] and LSRRM [3], but was renamed to LSRTM to correspond to the commonly used notation of the Simplified Reference Tissue Model SRTM.

Model Configuration and Assumptions

The model uses the same assumptions as the **Simplified Reference Tissue Model** (SRTM 153):

1. A reference tissue devoid of receptors exists which can be modeled by a single-tissue compartment model.

2. The distribution volume is the same for the tissue of interest and the reference tissue: $K_1/k_2=K_1'/k_2'$.

3. The kinetics in the receptor-rich tissue of interest is such that it is difficult to distinguish between the specific and the non-displaceable compartment; ie. the tissue TAC can be fitted by a 1-tissue compartment model with an apparent uptake rate constant $k_{2a} = k_2/(1+BP_{ND})$.
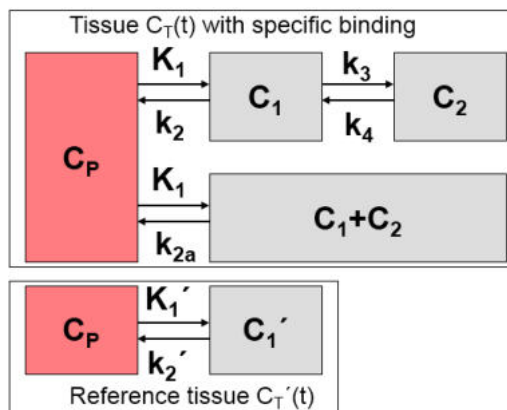
Additionally, it is assumed that at the onset of the activation, k_{2a} is increased by the amplitude γ of ligand displacement, and that the effect dies away with a decay constant τ. This behavior is described by a time-dependent k_{2a} as follows:

$$k_{2a}(t) = k_{2a} + \gamma\, h(t)$$

$$h(t) = \begin{cases} 0 & t < Begin \\ e^{-\tau u} & t \geq Begin,\ u = t - Begin \end{cases}$$

Operational Model Curve

Defining the ratio of tracer delivery R_1 as K_1/K_1', the following operational equation can be derived for the measured tissue TAC in a receptor-rich region:

$$C_{Model}(t) = R_1\, C_T'(t) + k_2\int_0^t C_T'(s)ds - k_{2a}\int_0^t C_T(s)ds - \gamma\int_0^t h(s)C_T(s)ds$$

From the parameters in the equation the binding potential BP_{ND} can be calculated as

$$BP_{ND} = \frac{k_2}{k_{2a}} - 1.0$$

The main outcome of the model, however, is the amplitude γ of ligand displacement, for which a t-score value and its p-value for a one-tailed t-test are also provided.

Parameter Fitting

The user has to define the **Activation** start time with the corresponding input parameter. The **Resampling** parameter defines the interpolation grid for the exponential convolution, which corresponds to the last integral term in the operational equation.

The parameters of the non-linear fitting procedure include **R1**, **k2**, **k2a**, **gamma** and **tau**. To reduce the number of fitted parameters **tau** is usually fixed at a value of 0.03min^{-1} (~23min half-life). From the fit parameters, **BPnd** is calculated as well as the **t-score** and the **p-value** of **gamma**.

References

1. Alpert NM, Badgaiyan RD, Livni E, Fischman AJ. A novel method for noninvasive detection of neuromodulatory changes in specific neurotransmitter systems. Neuroimage. 2003;19(3):1049-60. DOI

2. Christian BT, Lehrer DS, Shi B, Narayanan TK, Strohmeyer PS, Buchsbaum MS, Mantil JC. Measuring dopamine neuromodulation in the thalamus: using [F-18]fallypride PET to study dopamine release during a spatial attention task. Neuroimage. 2006;31(1):139-52. DOI

3. Ceccarini J, Vrieze E, Koole M, Muylle T, Bormans G, Claes S, Van Laere K. Optimized in vivo detection of dopamine release using 18F-fallypride PET. J Nucl Med. 2012;53(10):1565-72. DOI

6.4.6 Logan's Reference Tissue Model based on Average k2'

Model Configuration and Assumptions

Logan et al. [1] developed a reference tissue method for reversible receptor ligands which does not depend on a specific model structure of the reference tissue. Assuming the presence of reference region TAC $C_T'(t)$ with an average tissue-to-plasma clearance k_2', the target tissue TAC $C_T(t)$ is transformed and plotted as a function of the transformed reference TAC, as illustrated below.
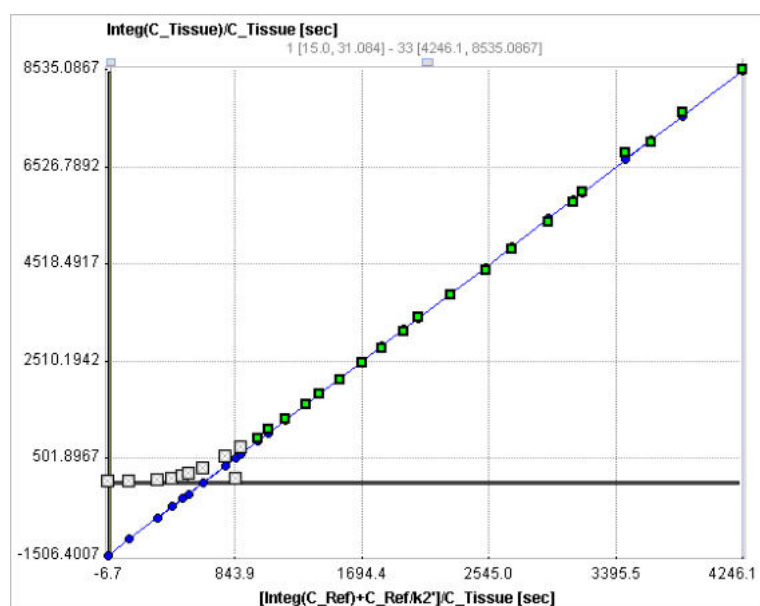
The operational equation resembles a linear equation with the distribution volume ratio (DVR = BP_{ND}+1) as the slope plus an error term which decreases over time. Therefore the late part starting

from a time t* of the plotted samples can be fitted by a regression line and the slope used for calculating BP_{ND}. The time t* can be determined as the time after which no further significant increases in slope are observed.

Operational Model Curve

The graphical plot of the **Logan Reference Tissue** method is described by the following equation with the form resembling a linear equation.

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = DVR\left[\frac{\int_0^t C_T'(\tau)d\tau + C_T'(t)/k_2'}{C_T(t)}\right] + b = (BP_{ND}+1)\left[\frac{\int_0^t C_T'(\tau)d\tau + C_T'(t)/k_2'}{C_T(t)}\right] + b$$

k_2' in the original publication was the population average k_2 determined for the reference tissue using blood sampling, but using the subject's own k_2' may be preferable.

Parameter Fitting

After switching to the **Logan Reference** model in PKIN a suitable reference region must be selected. **k2'** is an input parameter which must be manually entered, or estimated by using other models such as the MRTM or SRTM model. **Logan Reference** fits a linear regression to the tail of the plot starting at time **t***. Note that **t*** is specified in regular acquisition time, which is translated into the "funny time" of the x-axis and shown as the **Start** parameter. The result parameter of interest is the **BPnd** which is calculated from the slope.

A reasonable value of **t*** can be estimated by the based on the error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample such that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

> **Note:** The k_2' resulting from the SRTM or MRTM method might be a reasonable estimate for the average clearance rate k_2'. Therefore, when switching in PKIN from the SRTM or MRTM model to Logan Reference model, k_2' of those methods is automatically copied to k_2', in case **Model conversion** in the **Configuration** panel is enabled. See **above** [151] for recommendations how to estimate k_2'.

Reference

1. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL: Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 1996, 16(5):834-840. **DOI**

6.4.7   Ichise's Original Multilinear Reference Tissue Model (MRTM0)

Model Configuration and Assumptions

Starting from the operational equation of the blood-based **Logan plot** [167], Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1,2]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is transformed and plotted as a function of the transformed reference TAC, as illustrated below.

For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.

Operational Model Curve

The **MRTM0** model curve is described by

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = \frac{V_T}{V_T'}\frac{\int_0^t C_T'(\tau)d\tau}{C_T(t)} + \frac{V_T}{V_T'k'_2}\frac{C_T'(t)}{C_T(t)} + b$$

where V_T and V_T' are the total distribution volumes of $C_T(t)$ and $C_T'(t)$, k'_2 is the clearance rate constant from the reference region to plasma, and b is the intercept term, which becomes constant for $T > t^*$. The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. From the first coefficient the binding potential can be calculated by

$$BP_{ND} = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

Parameter Fitting

After switching to the **Ichise NonInvasive MRTM0** model a suitable reference region must be selected. It allows fitting a multi-linear regression to the operational equation within a range defined by the parameters **t*** and **End Lin**. The results are the three regression coefficients, and the derived binding potential **BPnd**.

A reasonable value of **t*** can be estimated by the based on the error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample such that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

For receptor ligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from t*=0, and b is equal to $(-1/k_2)$, where k_2 is the clearance rate constant from the tissue to plasma. Furthermore, $R_1 = K_1/K'_1$, the relative radioligand delivery, can be calculated from the ratio of the second and third regression coefficients.
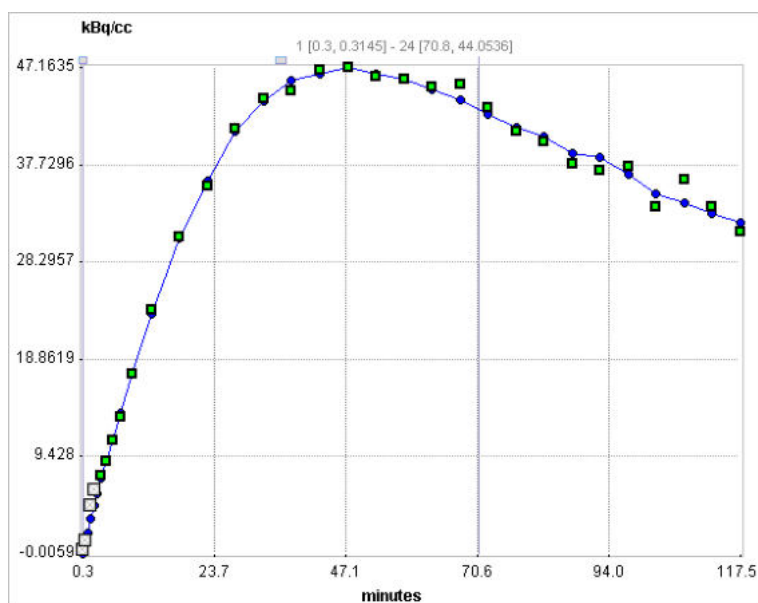
References

1. MRTM0: Ichise M, Ballinger JR, Golan H, Vines D, Luong A, Tsai S, Kung HF: Noninvasive quantification of dopamine D2 receptors with iodine-123-IBF SPECT. J Nucl Med 1996, 37(3):513-520.

2. Comparison of the MRTM and SRTM models: Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. **DOI**

6.4.8 Ichise's Multilinear Reference Tissue Model (MRTM)

Model Configuration and Assumptions

Starting from the operational equation of the blood-based **Logan plot** 167, Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is plotted as a function of the transformed tissue TACs as illustrated below. For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.

Operational Model Curve

To reduce noise-related bias effects arising in the MRTM0 method Ichise et al. applied a strategy known to be effective in reducing the noise-induced bias for the models requiring blood data. To this end the equation of the **MRTM0** 158 method was rearranged to remove the noisy tissue radioactivity term $C_T(t)$ from the independent variables. This approach resulted in a new method called MRTM with following operational equation for $C_T(t)$:

$$C_{Model}(t) = -\frac{V_T}{V_T'b}\int_0^t C_T'(\tau)d\tau + \frac{1}{b}\int_0^t C_T(\tau)d\tau - \frac{V_T}{V_T'k'_2 b}C_T'(t)$$

The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. The binding potential can then be calculated by dividing the first two regression coefficients

$$BP_{ND} = = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

Furthermore, division of the first by the third regression coefficient yields an estimate of k_2'.

Parameter Fitting

After switching to the **Ichise NonInvasive MRTM** model a suitable reference region must be selected. It allows fitting the multi-linear operational equation to the tissue TAC using the data segment starting from **t***. The results are the three regression coefficients, and the binding potential **BPnd** and **k2'**.

A reasonable value of **t*** can be estimated by the based on the error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample such that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

For receptor ligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from t*=0, and the clearance rate constant from the tissue to plasma k_2 is equal to the negative value of the second regression coefficient, -(1/b). Furthermore, $R_1 = K_1/K_1'$, the relative radioligand delivery, equals the third regression coefficient.

> **Note:** The reference methods MRTM2 and SRTM2 require k_2' as an input parameter. The k_2' resulting from the MRTM method above might be a suitable estimate. Therefore, when switching in PKIN from the MRTM model to MRTM2 or SRTM2, k_2' is automatically copied from MRTM, if the **Model conversion** option in the **Extras** panel is enabled.

Reference

1. Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. **DOI**

6.4.9 Ichise's Multilinear Reference Tissue Model 2 (MRTM2)

Model Configuration and Assumptions

Starting from the operational equation of the blood-based **Logan plot** [167], Ichise et al. derived three multi-linear reference tissue model variants MRTM0, MRTM and MRTM2 [1]. They all assume an initial equilibration time t* from which on the derived multi-linear relation holds. However, if kinetics in the target tissue can be described by a 1-tissue compartment model (an assumption required for the SRTM), all data can be used for the fitting (t*=0). Otherwise an adequate t* value has to be determined.

Assuming the presence of receptor-devoid reference region TAC $C_T'(t)$, the target tissue TAC $C_T(t)$ is plotted as a function of the transformed tissue TACs as illustrated below. For the calculation of BP_{ND} it is assumed that the non-displaceable distribution volumes in the tissue and reference regions are identical.

Operational Model Curve

When applied to noisy data such as single-pixel TACs in parametric mapping, the MRTM method still suffers from a high variability. Assuming a known value of the reference tissue clearance rate k_2' the MRTM operational equation can be reformulated as the MRTM2 operational equation:

$$C_{Model}(t) = -\frac{V_T}{V_T'b}\left(\int_0^t C_T'(\tau)d\tau + \frac{1}{k_2'}C_T'(t)\right) + \frac{1}{b}\int_0^t C_T(\tau)d\tau$$

with only two regression coefficients $V_T/(V_T'b)$ and $1/b$ for $T > t^*$. The multi-linear relationship above can be fitted using multi-linear regression, yielding three regression coefficients. The binding potential is then calculated from the ratio of the two regression coefficients as

$$BP_{ND} = = \frac{V_T}{V_T'} - 1.0 = DVR - 1$$

For receptor ligands with 1-tissue kinetics such as [11C]DASB the multi-linear equation is correct from $t^*=0$, and the clearance rate constant from the tissue to plasma k_2 is equal to the negative value of the second regression coefficient, $-(1/b)$. Furthermore, $R_1 = K_1/K_1'$, the relative radioligand delivery, equals the first regression coefficient divided by k_2'.

Parameter Fitting

After switching to the **Ichise NonInvasive MRTM2** model a suitable reference region must be selected. It allows fitting the multi-linear operational equation to the tissue TAC using the data segment starting from **t*** and a fixed value of **k2'** which needs to be specified. The results are the two regression coefficients, and the binding potential **BPnd**.

A reasonable value of **t*** can be estimated based on the error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample such that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

> **Note:** The k_2' resulting from the SRTM or MRTM method may be a suitable estimate for use in MRTM2. Therefore, when switching in PKIN from the SRTM or MRTM model to MRTM2, k_2' is automatically copied, if the **Model conversion** option in the **Extras** panel is enabled. Further suggestions how to obtain an adequate k2' value are given **above** [151].
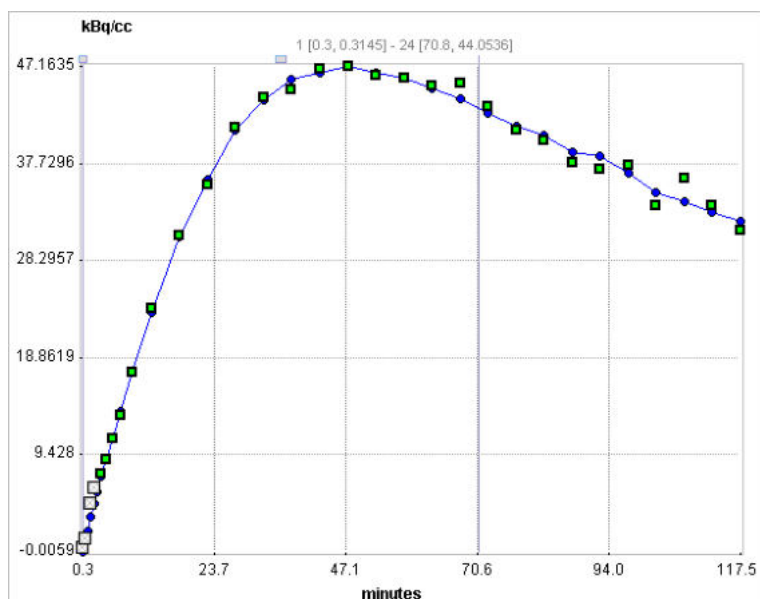
Reference

1. Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE: Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 2003, 23(9):1096-1112. **DOI**

6.4.10 Watabe's Reference Tissue Model with 2 Compartments

Model Configuration and Assumptions

The **2 Tissue Reference Tissue** method proposed by of Watabe [1] has been developed for ligands which do not follow the usual assumptions of the reference tissue models. Instead of a 1-tissue compartment model, the reference tissue is described by a 2-tissue model as illustrated below. The second compartment C_2' may represent specific or non-specific binding.
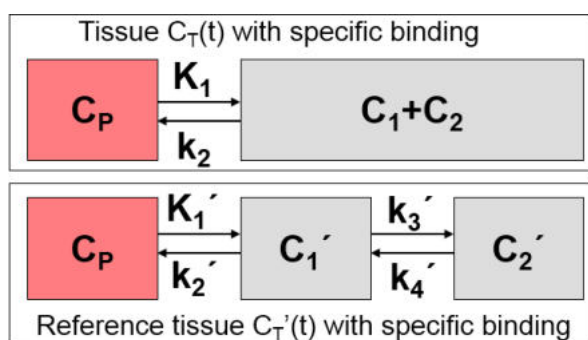
Operational Model Curve

Assuming that the non-specific distribution volume of both tissues is the same, the following operational equation for fitting the tissue TAC can be derived (see Millet et al [2], appendix C):

$$C_{Model}(t) = R_1 \left[C_T'(t) + a C_T'(t) \otimes e^{-(k_3'+k_4')t} + b C_T'(t) \otimes e^{-k_2 t} \right]$$

When the parameters k_2', k_3', and k_4' are fixed to constants determined with receptor-rich tissue, only R_1 and k_2 need to be fitted for estimating the binding potential BP_{ND}. The equation parameters and their relation to the model are given by:

$$a = \frac{k_3' k_2'}{k_3' + k_4' - k_2}$$

$$a = \frac{k_2^2 - k_2(k_2' + k_3' + k_4') + k_2' k_4'}{k_3' + k_4' - k_2} \ +$$

$$BP_{ND} = \frac{V_T}{V_T'} - 1 = \frac{K_1 k_2'}{K_1' k_2 (1 + k_3'/k_4')} - 1$$

For convolution with the exponentials, the reference tissue TAC $C_T'(t)$ is resampled on a regular grid, which can be specified by the **Resampling** parameter.

Parameter Fitting

After switching to the **2 Tissue Reference Model** a suitable reference region must be selected. The operational equation includes six fitting parameters: **R1**, **k2**, **k2'**, **k3'**, **k4'**. Per default, the fit boxes of **k2'**, **k3'** and **k4'** are off with the idea, that the values are determined externally. However, any of them may also be fitted. Fitting is performed using nonlinear techniques, and the main outcome is **BPnd**.

References

1. Original abstract: Watabe, H et al. The reference tissue model: Three compartments for the reference region. Neuroimage 11: S12.

2. Model description in Appendix C: Millet P, Graf C, Buck A, Walder B, Ibanez V: Evaluation of the reference tissue models for PET and SPECT benzodiazepine binding parameters. Neuroimage 2002, 17(2):928-942. **DOI**

6.4.11 Patlak Reference Tissue Model

The Patlak plot has been developed by Patlak and Blasberg [1] for tracers undergoing irreversible trapping. Most often it is applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with $k_4=0$.

However, this model structure is not necessary for the application of the method. It is sufficient to have any compartment in the system which binds irreversibly.

When the plasma activity is not available, the Patlak plot can be employed as a reference method provided that there exists some tissue wherein tracer is not irreversibly trapped. The procedure simply replaces the input curve by the reference tissue TAC.

Operational Model Curve

The Patlak plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Patlak plot using reference tissue is given by the expression

$$\frac{C_T(t)}{C_T'(t)} = K \frac{\int_0^t C_T'(\tau)d\tau}{C_T'(t)} + V$$

with the reference tissue TAC $C_T'(t)$. This means that the measured PET activity is divided by the reference tissue activity, and plotted at a "normalized time" (integral of the reference TAC from the injection time divided by the instantaneous reference activity). For systems with irreversible compartments this plot will result in a straight line after an equilibration time t*.
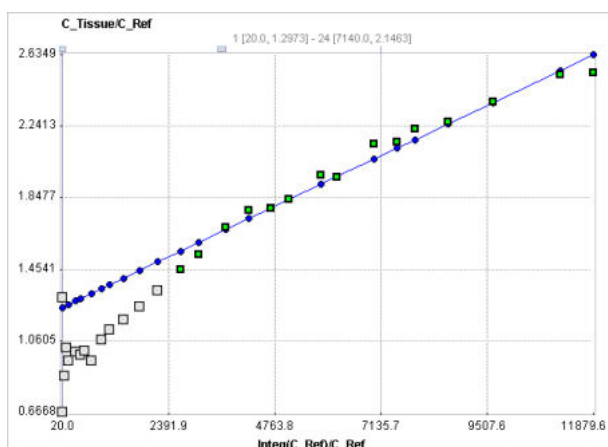
Under several assumptions, including a common K_1/k_2, the slope of the linear regression represents the following relation

$$slope = K = \frac{k_2 k_3}{(k_2 + k_3)(1 - K_{eq})}$$

with the equilibrium constant K_{eq}.

The reference Patlak plot has been applied for the FDOPA PET tracer for calculating an index of the influx K_i. Both the cerebellum and the occipital lobe have been used as the reference [2].

Parameter Fitting

The **Patlak Reference** model calculates and displays the transformed measurements as described by the formula above. It allows fitting a regression line to the data segment starting at time **t***. The results are the slope **K** and the **Intercept** of the regression line.

t* can be specified manually, or a value estimated using an error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression line and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

References:

1. Patlak CS, Blasberg RG: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab 1985, 5(4):584-590. DOI

2. Sossi V, Holden JE, de la Fuente-Fernandez R, Ruth TJ, Stoessl AJ: Effect of dopamine loss and the metabolite 3-O-methyl-[18F]fluoro-dopa on the relation between the 18F-fluorodopa tissue input uptake rate constant Kocc and the [18F]fluorodopa plasma input uptake rate constant Ki. J Cereb Blood Flow Metab 2003, 23(3):301-309. DOI

6.4.12 Multi-linear Reference Tissue Model for [11C]-MP4A (RLS)

Model Configuration and Assumptions

The **MP4A RLS (Nagatsuka)** model has been developed for the non-invasive quantification method (RLS) of the acetylcholinesterase (AChE) activity in the human brain from measurements with the ^{11}C-MP4A acetylcholine analog [1]. In contrast to reference methods for receptor tracers which use a reference devoid of specific binding, the present method uses a reference with very high AChE activity which immediately traps the tracer so there is no washout. $C_T(t)$ is the TAC from a cortical target region, and $C_T'(t)$ the TAC from the reference region (striatum or cerebellum). k_3 represents the rate of tracer hydrolysis by AChE.
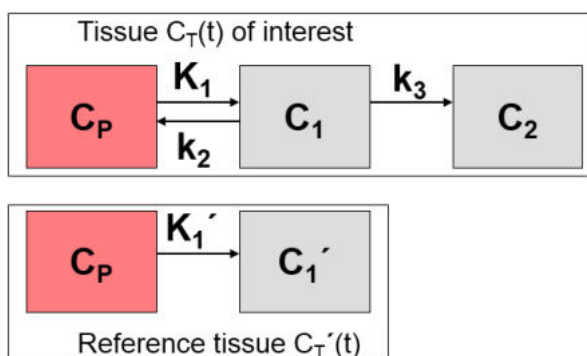
Operational Model Curve

By applying the method of Blomqvist, the following multi-linear equation is derived

$$C_{Model}(t) = p_1 C_T'(t) + p_2 \int_0^t C_T'(\tau)d\tau + p_3 \int_0^t C_T(\tau)d\tau$$

It can be fitted to $C_T(t)$ using multi-linear regression, yielding three regression coefficients from which three parameters of interest can be calculated:

$$R_1 = K_1 / K_1' = p_1$$
$$k_2 = -(p_3 + p_2 / p_1)$$
$$k_3 = p_2 / p_1$$

Parameter Fitting

After switching to the **MP4A RLS (Nagatsuka)** model a suitable reference region must be selected. The findings in different publications indicate that cerebellum yields more stable results than striatum, most likely due to the higher impact of motion on the signal from the small striatum than the large cerebellum.

While the regression coefficients represent the fitting parameters, the resulting rate constants are shown in the derived parameter section.

Reference

1. Nagatsuka Si S, Fukushi K, Shinotoh H, Namba H, Iyo M, Tanaka N, Aotsuka A, Ota T, Tanada S, Irie T: Kinetic analysis of [(11)C]MP4A using a high-radioactivity brain region that represents an integrated input function for measurement of cerebral acetylcholinesterase activity without arterial blood sampling. J Cereb Blood Flow Metab 2001, 21(11):1354-1366. **DOI**

6.5 Non-Compartmental Models

PKIN includes some additional models, which are neither explicit compartment nor reference models. They include the important linear regression methods **Logan Plot** and **Patlak Plot**, recent alternative methods for estimating the total distribution volume, as well as simple methods to quickly calculate ratios between tissue TACs and/or the plasma concentration.

Model Name	Description
Logan Plot [167]	Graphical analysis of reversible system to calculate the total distribution volume.
Ichise MA1 [172]	Reformulation of the Logan plot as a multilinear analysis to reduce noise-induced bias. Result is the total distribution volume.
Ichise MA2 [173]	Multilinear analysis derived from the two-compartment model. Results are the total as well as the specific distribution volume.
Patlak Plot [168]	Graphical analysis of irreversible system. Applied to FDG studies it allows to estimate glucose turnover.
Bolus/InfusionOptimization [181]	Based on a bolus study, the bolus/infusion ratio for an equilibrium study can be estimated
Area under Curve [191]	Calculates the integrals of the tissue TAC and the input curve, as well as their ratio.
Tissue/PlasmaRatio [192]	Calculate the ratio of tissue binding to plasma concentration in order to get an estimate of the total DV
Ratio Methods [193]	Calculate the ratio of specific binding to non-specific binding.
Retention Fraction [194]	Calculate the fraction of pased tracer which is accumulated in tissue
Fractal Dimension [195]	Calculation of the box-counting dimension of curves

π.pmod

6.5.1 Logan Plot

The Logan plot has been developed by Logan et al. [1] for ligands that bind reversibly to receptors and enzymes and is used for estimating the total distribution volume V_T. Its results can be interpreted with respect to the 1- and 2-tissue compartment models.
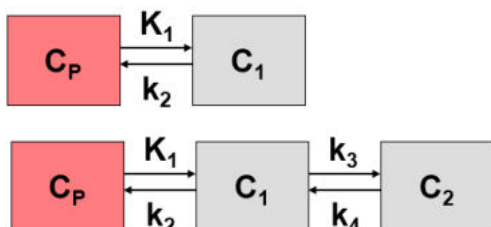

Operational Model Curve

The Logan plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Logan plot is given by the expression

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_T(t)} + b$$

with the input curve $C_p(t)$. This means that the tissue activity integrated from the time of injection is divided by the instantaneous tissue activity, and plotted at a "normalized time" (integral of the input curve from the injection time divided by the instantaneous tissue activity). For systems with reversible compartments this plot will result in a straight line after an equilibration time t*.
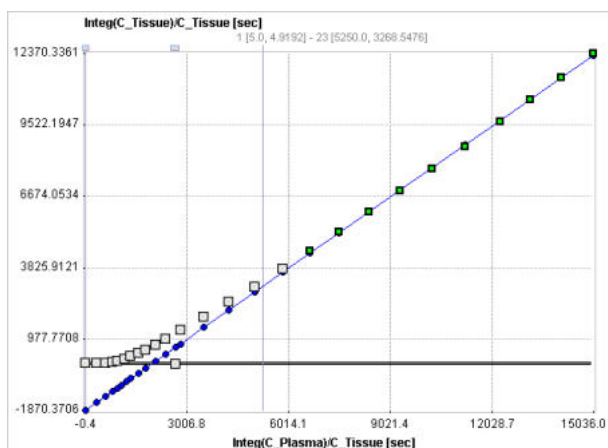
In the derivation of the Logan plot the PET signal is described as a sum of tissue activity plus a fractional plasma signal

$$C_{Model}(t) = C_T t) + v_P C_P(t)$$

unlike the operational equation of the compartment model. Under these premises the slope represents the total distribution volume V_T plus the plasma space v_p in the VOI, which is usually neglected. Alternatively an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

π.pmod

The relation of the slope to the parameters of the compartment models is given by

$$K \cong V_T = K_1/k_2 \qquad 1 - \text{tissue compartment model}$$
$$K \cong V_T = K_1/k_2(1 + k_3/k_4) \quad 2 - \text{tissue compartment model}$$

It has been found that the Logan plot is susceptible to noise in the data. Noise causes the true V_T to be underestimated, to a degree which not only depends on the noise level, but also on the local kinetics. The underestimation problem is particularly relevant in parametric mapping, where the pixelwise TACs suffer from a high noise level.

The reason for the underestimation effect is the fact that noise is not only present in the y-values (dependent variable) as the linear regression assumes, but also in the x-values (independent variable). To arrive at more accurate results it was therefore proposed to measure the residuals perpendicular to the regression line, rather than vertical to the x-axis [2].

Parameter Fitting

The **Logan Plot** model calculates and displays the measurements transformed as described by the formula above. It allows to fit a regression line within a range defined by the start time of the linear section **t***. The results are the distribution volume (slope) and the intercept. There is also an error criterion **Max Err** to fit **t***. For instance, if **Max Err** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**.

The regression line is calculated using the traditional and the perpendicular distances, resulting in the total distribution volumes **Vt** and **Vt_perpend**, respectively. It has been found that **Vt** has a tendency to underestimate the distribution volume at increasing noise levels. **Vt_perpend** shows less bias due to noise, but suffers from a somewhat increased variability.

References

1. Logan J, Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, MacGregor RR, Hitzemann R, Bendriem B, Gatley SJ et al: Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. J Cereb Blood Flow Metab 1990, 10(5):740-747. DOI

2. Varga J, Szabo Z: Modified regression model for the Logan plot. J Cereb Blood Flow Metab 2002, 22(2):240-244. DOI

6.5.2 Patlak Plot

The Patlak plot has been developed by Patlak et al. [1] for tracers undergoing irreversible trapping. Most often it is applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with k_4=0.
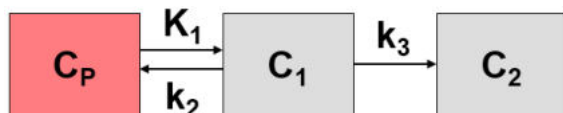

However, this model structure is not necessary for the application of the method. It is sufficient to have any compartment in the system which binds irreversibly.

Operational Model Curve

The Patlak plot belongs to a group of *Graphical Analysis* techniques, whereby the measured tissue TAC $C_T(T)$ undergoes a mathematical transformation and is plotted against some sort of "normalized time". The Patlak plot is given by the expression

$$\frac{C_T(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_P(t)} + V$$

with the input curve $C_p(t)$. This means that the measured PET activity is divided by plasma activity, and plotted at a "normalized time" (integral of the input curve from the injection time divided by the instantaneous plasma activity). For systems with irreversible compartments this plot will result in a straight line after an equilibration time t*.
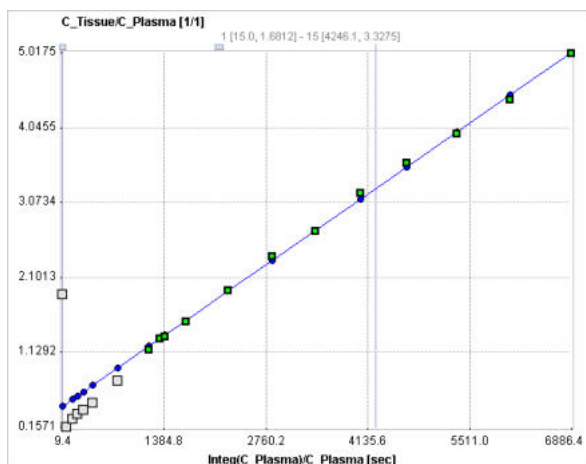
The slope K and the intercept V must be interpreted according to the underlying compartment model. For the FDG model mentioned, the slope K equals $K_1 k_3 / (k_2 + k_3)$ and represents the metabolic flux, while the intercept V equals $V_0 + vB$ with the distribution volume V_0 of the reversible compartment C_1 and the fractional blood volume vB.

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

Parameter Fitting

The **Patlak Plot** model calculates and displays the transformed measurements as described by the formula above. It allows fitting a regression line to the data segment starting at time **t***. The results are the **Slope** and the **Intercept** of the regression line.

t* can be specified manually, or a value estimated using an error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression line and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

For the analysis of FDG data, the **Lumped Constant** (LC) and the **Plasma glucose** level (PG) of the patient should be entered. The metabolic rate of glucose **MRGlu** is then obtained from the regression slope by

$$MRGlu = K_i \frac{PG}{LC}$$

Reference:

1. Patlak CS, Blasberg RG, Fenstermacher JD: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1983, 3(1):1-7. DOI

6.5.3 Spectral Analysis, vB

The **Spectral Analysis, vB** model allows performing a regular Spectral Analysis (SA) [17] given a TAC and an input curve according to Cunningham and Jones [1].

Operational Model Curve of Spectral Analysis

The operational equation of SA is given by

$$C_{Tissue}(t) = \sum_{i=1}^{N} a_i C_P(t) \otimes e^{-\beta_i t} = \sum_{i=1}^{N} a_i B_i(t)$$

$$C_{Model}(t) = (1-vB)\, C_{Tissue}(t) + vB\, C_{Blood}(t) \cong C_{PET}(t)$$

that is, tissue uptake is modeled as a sum of N possible tissue responses, and like for the compartment models a fixed blood volume fraction is supported.

Due to the constraint of first order tracer kinetics, the coefficients a_i and the decay constants b_i must be non-negative. In practice, a discrete set of the decay constants β_i is selected which covers the physiologically reasonable range, typically logarithmically spaced in the range $[10^{-5}, 1]\,sec^{-1}$. The corresponding tissue responses

$$B_i(t) = C_P(t) \otimes e^{-\beta_i t}$$

are the *Basis Functions* of spectral analysis. When fitting the operational equation above to a tissue TAC, the only unknowns are the coefficients a_i, because only a pre-defined set of discrete β_i values is considered. Therefore, the problem is that of a non-negative linear least squares estimation (NNLS) with the constraint of non-negative coefficients.

An advantage of SA is the fact that no particular compartment structure is imposed. Rather, its result can be used to estimate how many kinetic tissue compartments can be resolved by PET. To this end, the results are plotted as a spectrum with the selected decay constants β_i along the x-axis (as the "frequencies") and the estimated coefficients a_i along the y-axis (as the "amplitudes"). Because of the large range, $\log(\beta_i)$ is used in spectrum plotting rather than β_i. The number of peaks in this spectrum corresponds to the number of distinct compartments. A peak appearing to the far left (low frequency, slow component) indicates irreversible trapping. A peak to the far right (high frequency, fast component) corresponds to kinetics indistinguishable from the input curve, thus to vascular contributions. Intermediate peaks represent compartments which exchange reversibly with plasma or with other tissue compartments.

Parameter Fitting

In the **Spectral Analyis, vB** model **#Exponentials** determines the number of discrete β_i decay constants which are logarithmically spaced in the range between **Beta-min** and the **Beta-max.** There is no well-defined minimum value as in the case of decay-corrected TACs where it is equal to the decay constant of the isotope. **vB** is the fractional volume of whole-blood in the signal, which is subtracted before the SA. **Flux** is the influx into the irreversible compartment and the main result of the model. **vBest** is the remaining blood component after subtracting the whole-blood contribution.

Estimates of the tissue uptake constant **K1** and the total distribution volume **Vt** can be calculated based on the peaks found in the spectrum. **nPeak** is the number of peaks in the spectrum, whereby immediately neighboring spikes are grouped into a single peak.

The SA results can be visualized in 3 different ways with a corresponding radio button setting:

1. **Display TAC** shows the TAC together with the model curve calculated from the detected peaks.

2. **Display Spectrum** shows the peaks in the spectrum.

3. **Display unit IRF** shows the Impulse Response Function which depends on the **Exclude HF** setting.

Reference

1. Cunningham VJ, Jones T: Spectral analysis of dynamic PET studies. J Cereb Blood Flow Metab 1993, 13(1):15-23.

6.5.4   Spectral Analysis SAIF

The **Spectral Analysis SAIF** model allows performing a <u>Spectral Analysis (SA)</u> 17 with an explicit trapping compartment [1].

Operational Model Curve of Spectral Analysis

The operational equation for this type of SA is given by

$$C_{Tissue}(t) = a_0 \int_0^t C_P(t)dt + \sum_{i=1}^{N} a_i C_P(t) \otimes e^{-\beta_i t} = a_0 \int_0^t C_P(t)dt + \sum_{i=1}^{N} a_i B_i(t)$$

$$C_{Model}(t) = (1 - vB)C_{Tissue}(t) + vBC_{Blood}(t) \cong C_{PET}(t)$$

that is, tissue uptake is modeled as a sum of N possible tissue responses plus a flux a_0 into the irreversible compartment. Like for the compartment models a fixed blood volume fraction vB is supported.

Due to the constraint of first order tracer kinetics, the coefficients a_i and the decay constants b_i must be non-negative. In practice, a discrete set of the decay constants β_i is selected which covers the physiologically reasonable range, typically logarithmically spaced in the range $[10^{-5}, 1]$sec^{-1}. The corresponding tissue responses

$$B_i(t) = C_P(t) \otimes e^{-\beta_i t}$$

are the *Basis Functions* of spectral analysis. When fitting the operational equation above to a tissue TAC, the only unknowns are the coefficients a_i, because only a pre-defined set of discrete β_i values is considered. Therefore, the problem is that of a non-negative linear least squares estimation (NNLS) with the constraint of non-negative coefficients.

An advantage of SA is the fact that no particular compartment structure is imposed. Rather, its result can be used to estimate how many kinetic tissue compartments can be resolved by PET. To this end, the results are plotted as a spectrum with the selected decay constants β_i along the x-axis (as the "frequencies") and the estimated coefficients a_i along the y-axis (as the "amplitudes"). Because of the large range, $\log(\beta_i)$ is used in spectrum plotting rather than β_i. The number of peaks in this spectrum corresponds to the number of distinct compartments. A peak appearing to the far left (low frequency, slow component) indicates irreversible trapping. A peak to the far right (high frequency, fast component) corresponds to kinetics indistinguishable from the input curve, thus to vascular contributions. Intermediate peaks represent compartments which exchange reversibly with plasma or with other tissue compartments.

The Spectral Analysis with Iterative Filter (SAIF) approach uses a bandpass filter for selecting the real equilibrating compartments. The passband is defined by a range $[\beta_L, \beta_H]$. It is assumed that all $\beta_i < \beta_L$ are shifted noise components, and all $\beta_i > \beta_H$ shifted blood components. In an iterative process the following two steps are repeated

1. Subtract the noise and blood components (β_i outside [β_L, β_H]) from the signal, and estimate a_0 and vB.

2. Subtract the trapping and blood components (a_0 and vB) from the signal and estimate the equilibrating components.

The iteration is repeated until the residuals from step 1 and 2 are very similar.

Parameter Fitting

In the **Spectral SAIF** model **#Exponentials** determines the number of discrete β_i decay constants which are logarithmically spaced in the range between **Beta-min** and the **Beta-max.** There is no well-defined minimum value as in the case of decay-corrected TACs where it is equal to the decay constant of the isotope. The passband of equilibrating compartments is defined by **Beta-cutoff low** (β_L) and **Beta-cutoff high** (β_H). **vB** is the fractional volume of whole-blood in the signal, which is subtracted before the SA. **Flux** is the influx into the irreversible compartment and the main result of the model. **vBest** is the remaining blood component after subtracting the whole-blood contribution.

Estimates of the tissue uptake constant **K1** and the total distribution volume **Vt** of all reversible compartments can be calculated based on the peaks found in the spectrum. **nPeak** is the number of peaks in the spectrum, whereby immediately neighboring spikes are grouped into a single peak.

The SA results can be visualized in 3 different ways with a corresponding radio button setting:

1. **Display TAC** shows the TAC together with the model curve calculated from the detected peaks.

2. **Display Spectrum** shows the peaks in the spectrum.

3. **Display unit IRF** shows the Impulse Response Function which depends on the **Exclude HF** setting.

Reference

1. Veronese M, Bertoldo A, Bishu S, Unterman A, Tomasi G, Smith CB, Schmidt KC. A spectral analysis approach for determination of regional rates of cerebral protein synthesis with the L-[1-(11)C]leucine PET method. J Cereb Blood Flow Metab. 2010;30(8):1460-76. DOI

6.5.5   Ichise Multilinear Analysis MA1

Ichise's MA1 analysis method [1] is a technique for calculating the total distribution volume for receptor tracers with reversible binding. It is a further development of the Logan Plot [167] aimed at minimizing the bias induced by noise in the measurements.
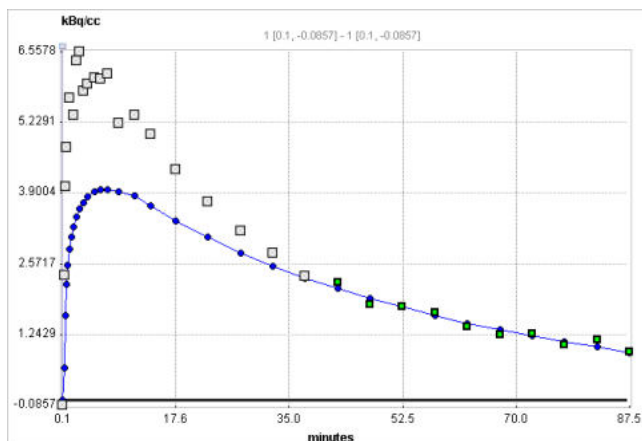
Operational Model Curve

The following bilinear relationship was derived

$$C_{Model}(t) = -\frac{V_T}{b} \int_0^t C_P(\tau) d\tau + \frac{1}{b} \int_0^t C_T(\tau) d\tau$$

where $C_T(t)$ represents the tissue time-activity curve, $C_P(t)$ the plasma activity, V_T the total distribution volume, and b the intercept of the Logan plot which becomes constant after an equilibration time t*.

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis as follows.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

Based on simulation and experimental data the authors show that MA1 demonstrates the largest bias reduction among several methods. Therefore they conclude, that MA1 is the method of choice for calculating the total distribution volume, if t* can accurately be defined.

Parameter Fitting

The bilinear regression is performed using singular value decomposition. The result are the two coefficients **VT/b** and **b**, from which **Vt** can easily be derived.

The MA1 method requires specification of the equilibration time as the **t*** parameter. As it equals the equilibration time of the Logan plot, it is possible to perform a [Logan plot] 167 first and use the resulting Logan **t***.

t* can also be estimated using an error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

Reference

1. Ichise M, Toyama H, Innis RB, Carson RE: Strategies to improve neuroreceptor parameter estimation by linear regression analysis. J Cereb Blood Flow Metab 2002, 22(10):1271-1281. DOI

6.5.6   Ichise Multilinear Analysis MA2

Ichise's MA2 analysis method [1] is another alternative technique developed to calculate the total distribution volume of reversible receptor systems with minimal bias. It is particularly suitable for tracers with slow kinetics and low to moderate noise.

The MA2 method has two advantages:

1. It is independent of an equilibration time, so that the data from the first acquisition can be included into the regression.

2. An estimate of the specific distribution volume is also obtained. The authors state, that although the method has been derived with the 2-tissue model, it still shows a good performance with the data representing only 1-tissue characteristics.

Operational Model Curve

Based on the 2-tissue compartment model equations the following multi-linear relationship was derived [34]:

$$C_{Model}(t) = p_1 \int_0^t \int_0^s C_P(\tau)d\tau ds + p_2 \int_0^t \int_0^s C_T(\tau)d\tau ds + p_3 \int_0^t C_T(\tau)d\tau + p_4 \int_0^t C_P(\tau)d\tau$$

where $C_T(t)$ represents the tissue time-activity curve, and $C_p(t)$ the plasma activity.
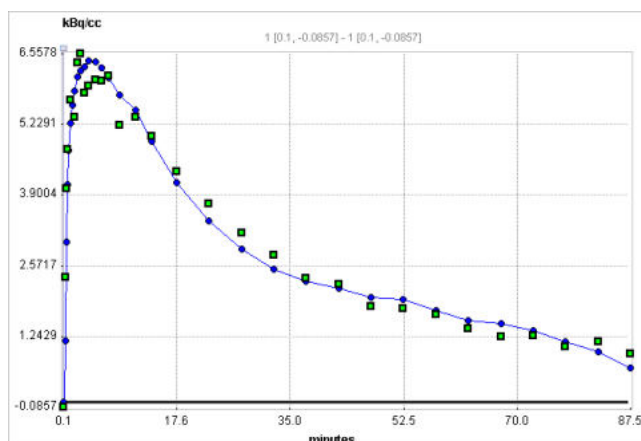
A multi-linear regression can be performed to calculate the four regression coefficients from the transformed data. The total distribution volume V_T is then calculated as the ratio of the first two regression coefficients, and the distribution volume of specific binding V_S by the expressions

$$V_T = -\frac{p_1}{p_2} \qquad V_S = \frac{-p_1(p_1 + p_3 p_4) + p_2 p_4^2}{p_2(p_1 + p_3 p_4)}$$

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis as follows.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

Parameter Fitting

The multi-linear regression is performed using a singular value decomposition, resulting in the 4 regression parameters **p1**, **p2**, **p3**, **p4**, and the derived distribution volumes **Vt** and **Vs**. Although no equilibration time is required for MA2, there is a **t*** parameter to disregard early samples from the regression as for the Logan plot 167 and MA1 172.

Reference

1. Ichise M, Toyama H, Innis RB, Carson RE: Strategies to improve neuroreceptor parameter estimation by linear regression analysis. J Cereb Blood Flow Metab 2002, 22(10):1271-1281. DOI

6.5.7   MLAIR (Multiple Linear Analysis for Irreversible Radiotracers)

The MLAIR method has been developed by Kim et al. [1] for tracers undergoing irreversible trapping. It is an alternative to the Patlak plot 168 analysis which is dependent on the specification of an equilibration time t* which may vary among tissues, and may suffer from bias when applied to noisy data. It has applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with k_4=0, and 11C-labeled MeNTI [1].
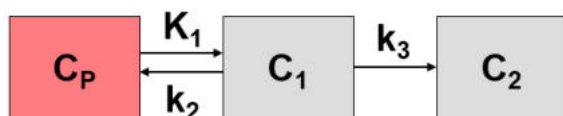
Operational Model Curve

The authors develop two approaches, both of which are included in the **Irreversible Ki (MLAIR)** model. The 2-tissue compartment model structure with $k_4=0$ is assumed. A blood volume fraction v_B is taken into account, but applied to the metabolite-corrected input curve $C_p(t)$ rather than the whole-blood activity.

The operational equation of method **MLAIR1** for the the measured tissue TAC $C_T(t)$ is given by

$$C_{Model}(t) = P_1 C_P(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 \int_0^t C_T(\tau)d\tau + P_4 \int_0^t \int_0^\tau C_P(s)ds d\tau$$

The linear coefficients are related to the model parameters as follows, allowing to calculate the influx K_i from P_3 and P_4.

$$
\begin{aligned}
P_1 &= v_B & P_3 &= -(k_2 + k_3) \\
P_2 &= K_1 + k_2 v_B + k_3 v_B & P_4 &= K_1 k_3 \\
K_i &= -P_4/P_3
\end{aligned}
$$
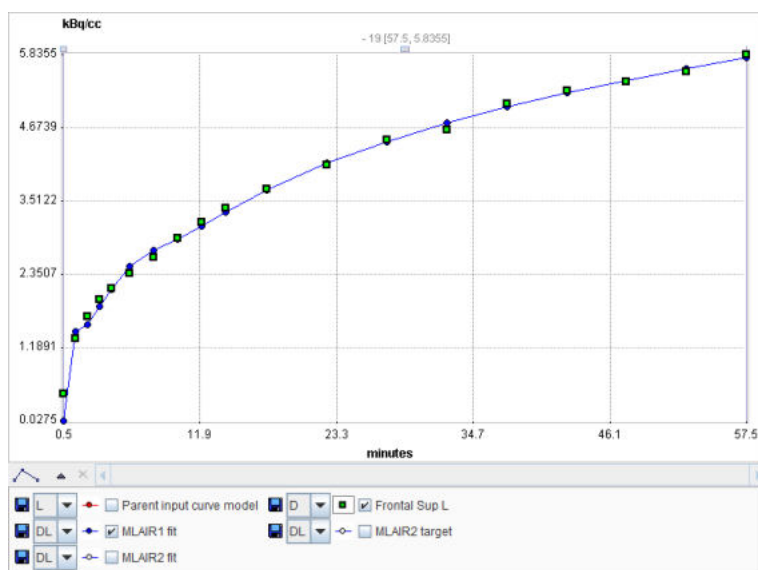
In order to avoid the P_4/P_3 division of MLAIR1 which might intorduce artefacts for noisy data, a second second multilinear operational equation MLAIR2 was developed which estimates K_i as a direct regression parameter. **MLAIR2** has the following operational equation for the integrated tissue activity curve:

$$C_{Model}(t) = \int_0^t C_T(\tau)d\tau = P_1 C_P(t) + P_2 \int_0^t C_P(\tau)d\tau + P_3 C_T(t) + P_4 \int_0^t \int_0^\tau C_P(s)ds d\tau$$

$$
\begin{aligned}
P_1 &= v_B/(k_2 + k_3) & P_3 &= -1/(k_2 + k_3) \\
P_2 &= K_1/(k_2 + k_3) + v_B & P_4 &= K_i
\end{aligned}
$$
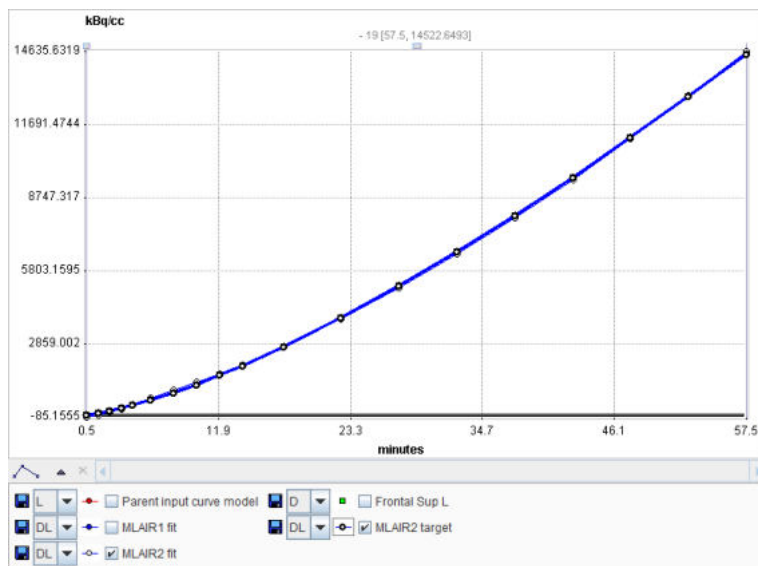
Parameter Fitting

As soon as the **Irreversible Ki (MLAIR)** model is selected it fits the MLAIR1 and MLAIR2 model curves to the data using singular value decomposition and shows the regression coefficients. The parameter of interest is K_i which is calculated with both methods: **Ki(MLAIR1)** and **Ki(MLAIR2).**

The curve area initially shows the tissue TAC together with the **MLAIR1** fit, whereas the MLAIR2-related curves are hidden because the have a completely different dynamic range. However, they can easily be shown by enabling the respective check boxes in the curve control area, as illustrated above.

Reference:

1. Kim SJ, Lee JS, Kim YK, Frost J, Wand G, McCaul ME, Lee DS: Multiple linear analysis methods for the quantification of irreversibly binding radiotracers. J Cereb Blood Flow Metab 2008, 28(12):1965-1977. DOI

6.5.8   RE-GP Analysis

In 2009 Zhou et al. introduced a new graphical method, the Relative-Equilibrium (RE) plot [1]. It can be applied with a plasma input curve for the calculation of the distribution volume, and with a reference tissue curve for the calculation of the binding potential. It was shown with Raclopride data and with simulations, that unlike the Logan plot the RE plot is not suffering from bias due to high noise levels. As a consequence, the results obtained with VOI-averaged TACs is consistent to the results obtained in pixel-wise applications.

However, it was found that violation of the relative equilibrium condition did introduce bias. To compensate this bias Zhou et al [2] combined the RE plot with the Patlak plot in a bi-graphical manner called the **RE-GP Analysis.**

Operational Model Curve

The operational equation of the RE Plot is given by:

$$\frac{\int_0^t C_T(\tau)d\tau}{C_P(t)} = V_{T\,RE}\frac{\int_0^t C_P(\tau)d\tau}{C_p(t)} + \alpha$$
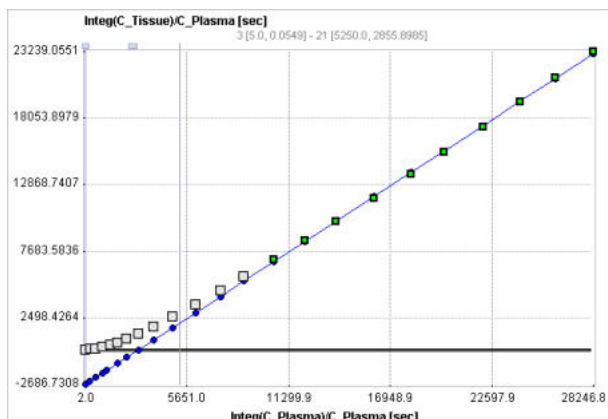
For the RE plot to be applicable there must exist a time t* after which two conditions are fulfilled:

1. The plasma input curve must be mono-exponential. This condition can be verified by fitting a single exponential to the late part of the plasma curve on the **Blood** tab of PKIN.

2. The ratio of C_T/C_p is constant. This condition can be verified by switching the **KM** model to the **Tissue/Plasma Ratio** model.

Under these conditions the tracer in all tissue compartments reaches equilibrium relative to plasma. Note that the conditions must be verified explicitly, because the linear appearance of the RE plot is not a sufficient criterion.

Violation of the relative equilibrium condition above introduces bias. To compensate this bias the RE plot was combined with the Patlak plot

$$\frac{C_T(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau)d\tau}{C_P(t)} + \beta$$
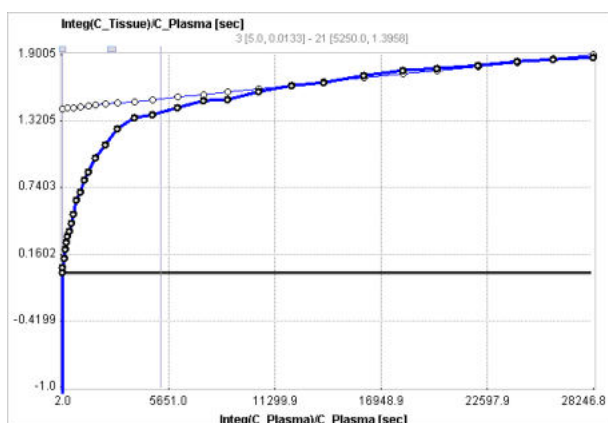
using the same t* for fitting two respective regression lines. A consistent and unbiased distribution volume is then obtained by combining the slopes and intercepts of the two plots:

$$V_T = V_{TRE} - \frac{\alpha K}{\beta}$$

For the pixel-wise application of the RE-GP Analysis the results of the Patlak plot are smoothed, so that the calculation turns into

$$V_T = V_{TRE} - \frac{\alpha K_s}{\beta_s}$$

where K_s and β_s are obtained from spatially smoothed maps of K and β.

Parameter Fitting

The **RE-GP Analysis** model calculates and displays the measurements transformed as described by the RE plot formula above. It allows fitting a regression line using the data points after a time **t***. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**.

If **t*** is changed to define a new data segment, the program finds the closest acquisition start time, fits the two regression lines to the RE plot and the Patlak plot, and updates the calculated parameters. The main outcome is the distribution volumes calculated with the RE-GP analysis (**Vt-REGP**). For a comparison, Vt calculated with the RE plot alone (**Vt-RE**) is also shown.

Per default, only the curves of the RE plot and its regression line are shown in the curve area. However, the Patlak plot and its regression line can also be visualized by enabling their boxes in the curve control area. Note that the values of the Patlak plot may have a very different dynamic range than the RE plot. Therefore it is recommended switching off the RE curves when switching on the Patlak ones.

References

1. Zhou Y, Ye W, Brasic JR, Crabb AH, Hilton J, Wong DF: A consistent and efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. Neuroimage 2009, 44(3):661-670. DOI

2. Zhou Y, Ye W, Brasic JR, Wong DF: Multi-graphical analysis of dynamic PET. Neuroimage 2010, 49(4):2947-2957. DOI

6.5.9 Ito Plot

In 2010 Ito et al. introduced a new graphical method for the analysis of reversible receptor ligand binding [1]. It is applied with a plasma input curve for the calculation of the total distribution volume V_T, the distribution volume of the nondisplaceable compartment V_{ND}, and therefore also allows calculation of the binding potential BP_{ND}. Furthermore, the shape of the plot gives an indication whether there the tissue includes is specific binding or not not.

Operational Model Curve

The equation of the graphical plot called is given by the equation

$$\frac{C_T}{\int_0^t C_P(\tau)d\tau} = a - b \frac{\int_0^t C_T(\tau)d\tau}{\int_0^t C_P(\tau)d\tau}$$

The following cases can be distinguished:

1. The plot is a straight line, indicating the *absence* of specific binding. In this case the line equation parameters have the following interpretation in terms of a 2-tissue compartment model:
   a = K_1 (y-intercept), b = k_2 (slope), and the x-intercept equals V_{ND}.

2. The plot has a curved shape as illustrated below, indicating the presence of specific binding. In this case two regression lines are fitted to the plot: a line to the early part within a short time segment T_1 to T_2, and a line to the end part after an equilibration time t*. The parameters of the resulting lines can be interpreted as follows:
   Early line: $a_1 = K_1$, $b_1 = k_2$, x-intercept = V_{ND} of a 2-tissue compartment model.
   Late line: $a_2 = K_1'$, $b_2 = k_2'$, x-intercept = V_T of a 1-tissue compartment model.
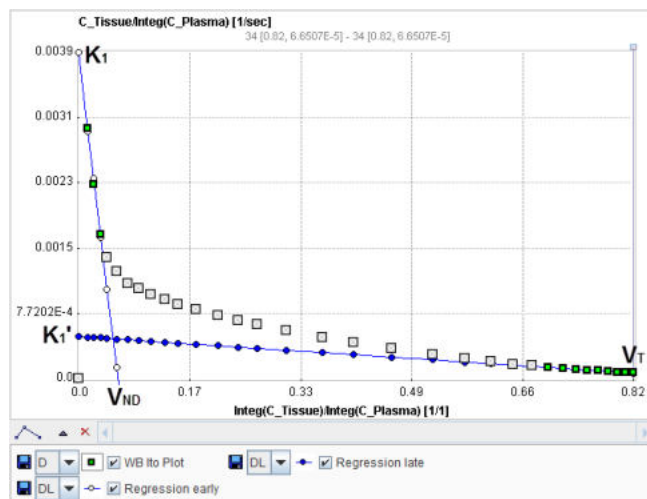
The binding potential can finally be calculated by $BP_{ND} = (V_T - V_{ND})/V_{ND}$

Parameter Fitting

The **Ito Plot** model calculates and displays the measurements transformed as described by the Ito plot formula above. It allows fitting two regression lines as follows:

1. The first regression line is fitted within the data segment specified by the times **T1** and **T2** (in acquisition time).

2. The second regression line is fitted to the late data segment starting at equilibration time **t***.

If any of the times is changed to define a new data segment, the program finds the closest acquisition start time, fits the two regression lines, and updates the calculated parameters.

t* can be specified manually, or a value estimated using an error criterion **Max Err**. For instance, if **Max Err.** is set to 10% and the fit box of **t*** is checked, the model searches the earliest sample so that the deviation between the regression line and all measurements is less than 10%. Samples earlier than the **t*** time are disregarded for regression and thus painted in gray. Note that **t*** must be specified in real acquisition time, although the x-axis units are in "normalized time". The corresponding normalized time which can be looked up in the plot is shown as a non-fitable result parameter **Start**. In order to apply the analysis to the same data segment in all regions, please switch off the fit box of **t***, propagate the model with the **Copy to all Regions** button, and then activate **Fit all regions**.

Per default, only the Ito Plot and the late regression line is shown in the curve area. However, the early regression line can also be visualized as illustrated above by enabling its box in the curve control area.

References

1. Ito H, Yokoi T, Ikoma Y, Shidahara M, Seki C, Naganawa M, Takahashi H, Takano H, Kimura Y, Ichise M et al: A new graphic plot analysis for determination of neuroreceptor binding in positron emission tomography studies. Neuroimage 2009, 49(1):578-586. DOI

6.5.10 Partial Saturation Method, Data-driven

Wimberley et al. [1] have developed a data driven strategy for the partial saturation approach (ddPSA) [2] for determining reliable regional estimates of receptor density B_{avail} and in vivo affinity $1/appK_D$. It is a reference tissue approach applicable to 11C raclopride which makes it ideal for use in longitudinal studies of neurodegenerative diseases in the rodent.

Operational Equation

The non-linear 2-tissue compartment model with saturable specific binding is illustrated below.
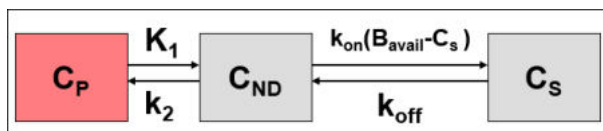
The differential equations for a target tissue can be rearranged [1] to

$$\frac{C_S(t)}{C_{ND}(t)} = \frac{B_{avail} - C_S(t)}{appK_D} - \frac{dC_S(t)}{dt} \frac{1}{k_{off} C_{ND}(t)} = \frac{B_{avail} - C_S(t)}{appK_D} - DET(t)$$

where C_S represents the concentration of specifically bound ligand, C_{ND} the concentration of non-displaceable ligand, k_{off} the dissociation constant (taken from in vitro data) and $appK_D$ is the reciprocal of the in vivo receptor-ligand affinity. DET is a term related to the dynamic equilibrium of the system.

The ddPSA approach uses the scaled concentration of a reference tissue as an approximation of the C_{ND} in the target tissue
$C_{ND}(t) = r\, C_{Ref}(t)$
where r is determined in a presaturation study.

The time course $C_S(t)$ is then calculated by
$C_S(t) = C_T(t) - C_{ND}(t)$
where $C_T(t)$ represents the activity concentration in the target tissue.

Using $C_S(t)$, $C_{ND}(t)$ and the in vitro k_{off}, DET(t) is plotted. When the DET is negligible compared to the C_S/C_{ND} value, the PET scan is in a dynamic equilibrium state and the C_S and C_{ND} values can be used for in estimation of B_{avail} and $appK_D$.

Parameter Fitting

The **Partial Saturation, data-driven** model is a reference tissue model. The scale factor **r** for the reference tissue is an input parameter to be determined in a separate experiment. The specific activity **Spec. Act.** is required for converting kBq/cc data to pmol/ml. **tstart** and **tend** define the range within which the data is considered for the fit. **koff** is the in vitro dissociation constant, and **Threshold** defines the cutoff value for DET relative to C_S/C_{ND}.

The fitting procedure switches off all time points with |DET(t)| above the threshold, and estimates **Bavail** and **appKD**. As illustrated below, the various curves involved in the model calculations can be enabled for display, for instance DET(t).
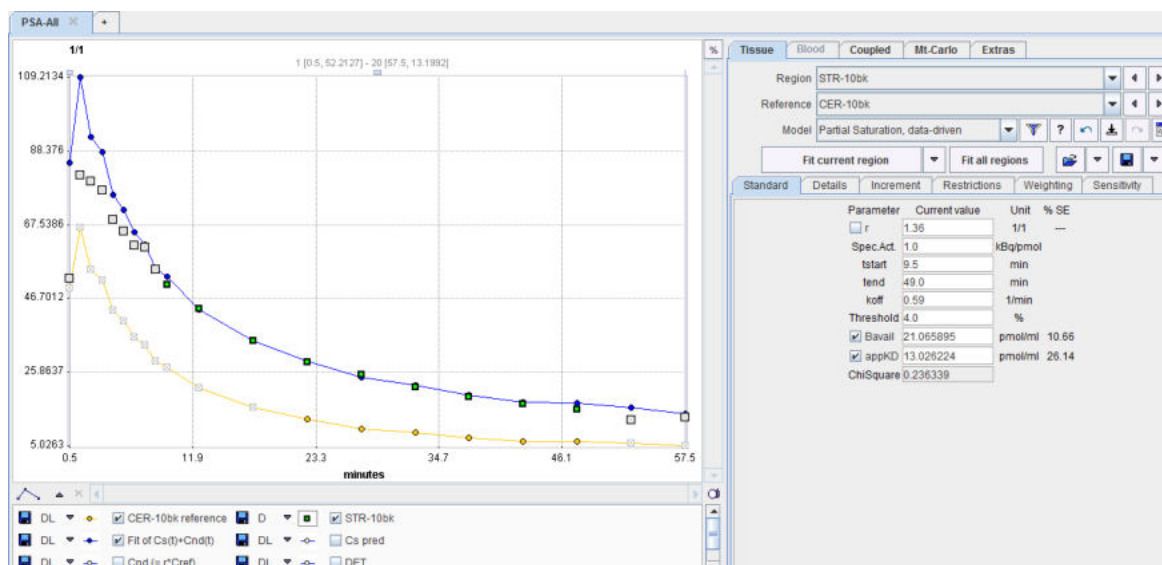
Reference

1. Wimberley CJ, Fischer K, Reilhac A, Pichler BJ, Gregoire MC. A data driven method for estimation of B(avail) and appK(D) using a single injection protocol with [(1)(1)C]raclopride in the mouse. Neuroimage. 2014;99:365-76. DOI

2. Delforge J, Spelle L, Bendriem B, Samson Y, Syrota A. Parametric images of benzodiazepine receptor concentration using a partial-saturation injection. J Cereb Blood Flow Metab. 1997;17(3):343-55.

6.5.11 Bolus/Infusion Optimization

When a compartment system has equilibrated, the total distribution volume can be calculated easily as the ratio of tracer concentration in tissue to the metabolite-corrected plasma concentration with a single static scan. It has been found that the time required to reach equilibrium can be shortened by an optimized tracer delivery. A setup which does not require a sophisticated tracer delivery system is to apply an initial bolus and continue with a constant infusion.

Carson et al. [1] have developed a method to optimize the ratio between the activity given as the initial bolus and the activity level of the subsequent infusion for quickly reaching an equilibrium (Appendix B in [1]). It is assumed that tissue TACs as well as the input curve have been measured beforehand in a bolus experiment. Ideally then, the measured activities represent the impulse response of the system. Under this assumption it is possible to calculate the tissue response for any given input curve by just convolving the TACs with the input curve.

Operational Model Curve

For a bolus and infusion (B/I) experiment the input function can be described as an initial impulse followed by a step function, and the convolution can be analytically solved. The resulting model curve

$$C_{Model}(t) = \frac{K_{bol}C_T(t) + \int_0^t C_T(\tau)d\tau}{K_{bol} + T}$$

is a function of the bolus fraction and the infusion duration. K_{bol} [min] defines the dose of the bolus expressed as minutes of infusion, and T is the total duration of the infusion (end of last frame).

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$
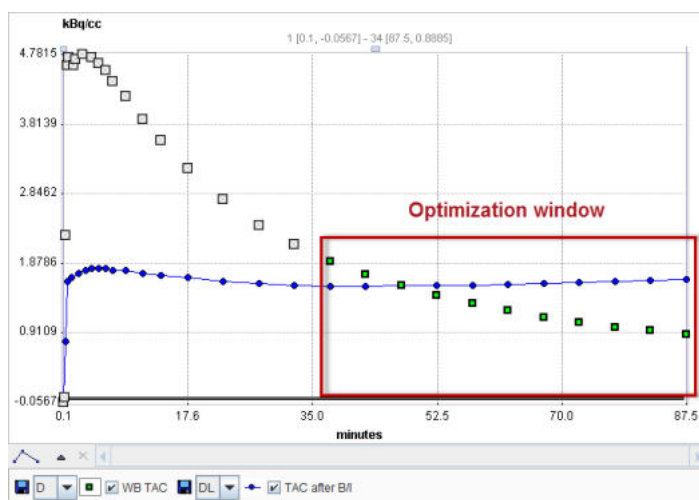
Parameter Fitting

It is assumed that the data of a bolus study has been loaded. When the **Bolus/Infusion Opt** model is selected, the expected tissue activity according to the formula above is calculated using the default parameters, and shown as the model curve.

Kbol can be estimated. The user has to enter a reasonable equilibration time as the input parameter **Start Equilibr.** When **Fit current region** is activated, the optimal **Kbol** is calculated. The criterion for an equilibrium is that the calculated activities from **Start Equilibr** to the end of the scan are as constant as possible. Using the duration of the current data, the % **Fraction** of the dose in the syringe is displayed which is to be injected as the initial bolus.

Also, please note the following:

1. The same formulation holds for both TACs and input curves. However, K_{bol} can only be fitted with the TAC curve, not the input curve. For the blood curve, the **Bolus/Infusion Opt** model is only usable for visualizing the plasma response with an entered K_{bol} value which was obtained in TAC fitting.

2. If the **Bolus/Infusion Opt** model is applied to a TAC and the **Fit blood** is enabled in the **Extras** panel, the **Bolus/Infusion Opt** model is also applied to the plasma curve during the fit using the plasma model curve. Therefore the *plasma model should be an interpolation model, NOT THE B/I model!***Kbol** is a common parameter in the fit, and the criterion is that both the expected TAC and the expected input curve are constant.

3. The **Bolus/Infusion Opt** model can be used for coupled fitting to find the optimal dose for several tissues. In a coupled fit, only the TACs are used, and the input curve is currently neglected (as opposed to 2).

4. The residual weighting of all curves involved in the fit should be set to constant weighting.

Reference

1. Carson RE, Channing MA, Blasberg RG, Dunn BB, Cohen RM, Rice KC, Herscovitch P: Comparison of bolus and infusion methods for receptor quantitation: application to [18F] cyclofoxy and positron emission tomography. J Cereb Blood Flow Metab 1993, 13(1):24-42. DOI

6.5.12 Cumulated Activity (OLINDA, IDAC)

The **Cumulated Activity (OLINDA, IDAC)** model performs pre-processing steps for the calculation of the absorbed dose from diagnostic or therapeutic radiopharmaceuticals. Given the time-course of the activity in a volume of tissue, it calculates the the *Normalized Cumulated Activity* [1] (OLINDA *Residence Time*). The normalized cumulated activity represents the total number of disintegrations which have occurred during an integration time per unit administered activity. Ideally, integration is performed from the time of administration to infinity.

The normalized cumulated activity values resulting from the **Cumulated Activity (OLINDA, IDAC)** model can serve as input to a program such as OLINDA [2] or IDAC2.1 for the actual calculation of the absorbed organ doses.

Note that all steps required for the analysis of dosimetry data are explained in detail in the PMOD Workflow for Dosimetry Preprocessing application guide.

Operational Equations

Given an activity A_0 applied to a subject, and a measured (NOT decay corrected) activity A(t) in an organ, the Normalized Cumulated Activity τ is calculated by

$$\tau = \frac{\int_0^\infty A(t)dt}{A_0}$$

Note that the unit of τ is usually given as [Bq·hr/Bq]. The measured part of the organ activity can easily be numerically integrated by the trapezoidal rule. For the unknown remainder of A(t) till infinity it is a conservative assumption to apply the radioactive decay of the isotope. This exponential area can easily be calculated and added to the trapezoidal area. Alternatively, if the measured activity curve has a dominant washout shape, a sum of exponentials can be fitted to the to the measured data and the entire integral algebraically calculated.

The **Cumulated Activity (OLINDA, IDAC)** model in PKIN supports both the trapezoidal integration approach as well as the use of fitted exponentials. It furthermore supports some practicalities such as
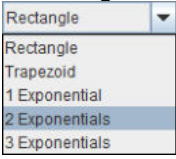
- conversion of an average activity concentration in [kBq/cc] to VOI activity in [Bq] by multiplication with the VOI volume;

- reversion of decay correction;
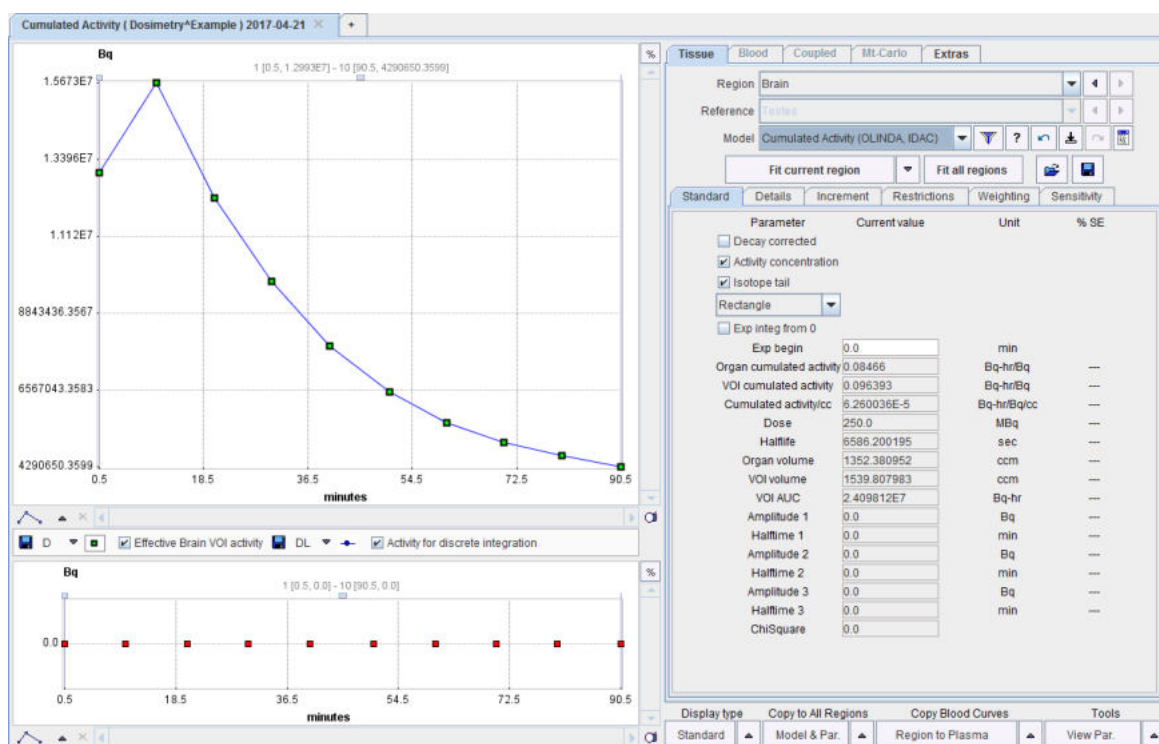
Model Input Parameters

The **Cumulated Activity (OLINDA, IDAC)** model has 4 input parameters which need to be specified interactively by the user. These settings can easily be propagated from one region to all others with the **Model & Par** button.

Decay corrected	Check this box if the loaded curves have been decay corrected as is usually the case for PET imaging studies. The **Halflife** of the radioisotope will be used to undo the decay correction.
Activity concentration	Check this box if the loaded curves represent activity concentration rather than the total activity in a region. The **volume** of the region will be multiplied with the signal to calculate and show the activity in [Bq].
Isotope tail	Check this box to use the radioactive decay shape for the integration from the end of the last frame to infinity. This option is only relevant if exponentials are fitted to the measurement. For the **Rectangle** and **Trapezoid** methods it will always be enabled. For the exponentials it will also be enabled if the exponential halftime is longer than the isotope half-life.

Integration Selection	The integration method can be selected in the option list: Rectangle ▼ Rectangle Trapezoid 1 Exponential 2 Exponentials 3 Exponentials The **Rectangle** method is the natural selection for PET values which represent the time average during the frame duration. If there are gaps between the PET frames, the uncovered area is approximated by the trapezoidal rule. The **Trapezoid** method uses trapezoidal areas between the frame mid-times. With an **Exponential** selection, the specified number of decaying exponentials is fitted to the measurements, and used for analytical integration. Note that samples marked as invalid are neglected in the fit.
Exp integ from 0	Check this box to use the exponential from time zero for the integration. If the box is unchecked, rectangular integration is used for samples before **Exp begin**.
Exp begin	Defines the time (frame mid), from when on the exponentials are fitted to the measurement.

Editing of Constituents

Depending on the import of the activity curves, isotope and activity information may or may not be available. They can be edited in the **Patient and Study Information** window as illustrated below. Activate **Edit Patient** in the **Tools** list, select **SUV PARAMETERS**, and enter **Radionuclide half-life** and **Pre-injected tracer activity**. Note that the activity needs to be calibrated to time 0 of the activity curve.
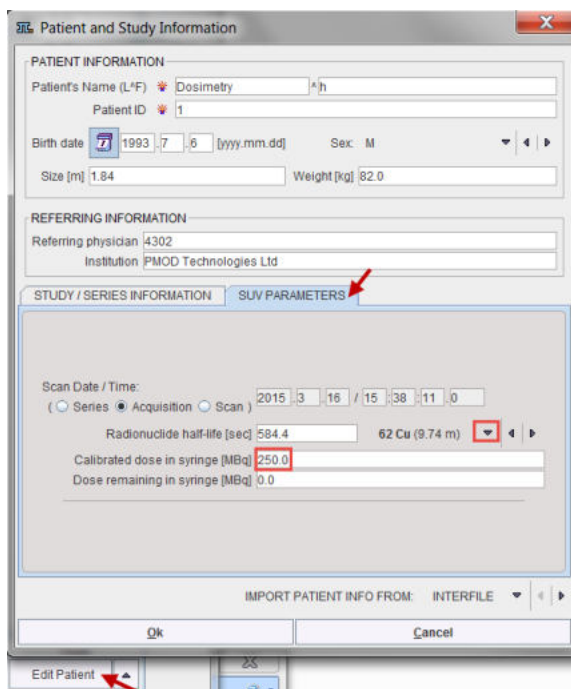
The regional VOI volume is available if the TAC was generated in PMOD's View tool and transferred to PKIN. Often, not the entire volume of the organ can be outlined, because it is not clearly visible, or because (like muscle), it is not compact. In this case, standard organ volumes can be used for extrapolating VOI uptake to organ uptake. An organ can be assigned to a defined VOI as illustrated below:

1. Select the VOI in the list.

2. Open the VOI properties editor, and select the **Set** button.

3. Select an appropriate name list. For instance, the **OLINDA (Adult male)** contains the organ definitions (name, volume, mass) for the adult male phantom in OLINDA.

4. Choose the organ from the list. The predefined **ORGAN volume** and **mass** are shown and may be edited.

5. Close with the **Set VOI name and color** button.
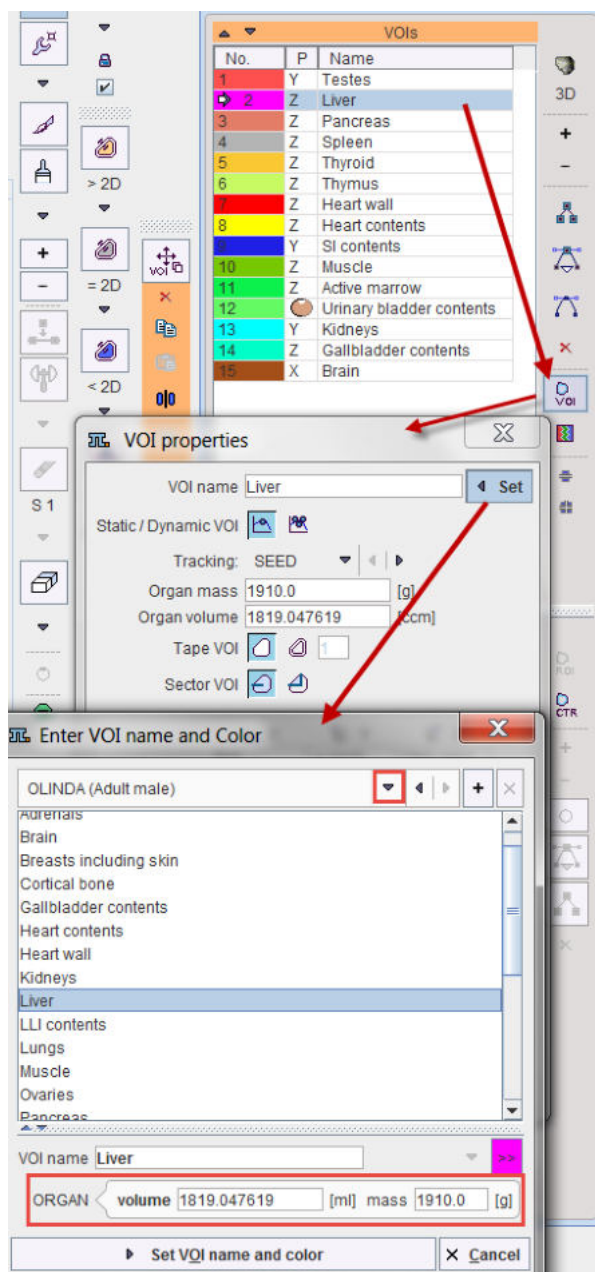
An alternative approach is to edit the VOI and organ volumes as follows:

1. Activate **Edit Data** in the **Tools** list

2. Select a region in the upper list.

3. Choose **Edit volume** from the curve tools

4. Enter the **Volume** of the VOI in the dialog window.

5. Change The **Organ Volume** in the lower part. (currently, Organ mass is not used for the calculation).

6. Close the **PKIN data explorer** with **Ok**.
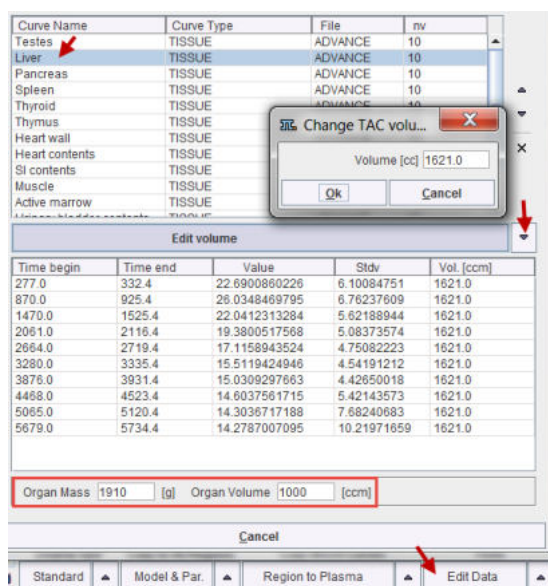
Model Output Parameters

As soon as the **Fit Region** button is activated, the fits and calculations are performed, resulting in a list of parameters:

Organ cumulated activity [Bq·hr/Bq]	Total number of disintegrations in the organ volume from time 0 until infinity per unit injected activity. This is the main result and equal to **Cumulated activity/cc*Organ Volume**. Note that it is zero as long as the **Organ volume** is not defined.
VOI cumulated activity [Bq·hr/Bq]	Total number of disintegrations in the regional VOI volume from time 0 until infinity per unit injected activity, calculated as **VOIAUC**/**Activity**.
Cumulated activity/cc [Bq/cc·hr/Bq]	Total number of disintegrations per unit volume and unit injected activity. Equal to **VOI cumulated activity**/**VOI Volume**.
Dose [MBq]	Administered activity at the time of scan start. Shown for verification only. Can be changed via Edit Patient [103].
Halflife [sec]	Isotope halflife. Shown for verification only. Can be changed via Edit Patient [103].
Organ Volume [ccm]	Volume of the organ which corresponds to the regional VOI. Shown for verification only. Can be changed via Edit Data [102].
VOI Volume [ccm]	Volume of the VOI in which the uptake is measured. Shown for verification only. Can be changed via Edit Data [102].
VOI AUC [Bq·hr]	Integral of the VOI activity curve from time 0 till infinity.
Amplitude 1, **2**, **3 [Bq]** **Halftime 1**, **2**, **3 [min]**	Amplitudes and halftimes of the fitted exponentials. In the case of 1 exponential a linear regression is applied, whereas iterative fitting is used with 2 or 3 exponentials.

Generate Output File for Dosimetry Programs

After the **Cumulated Activity (OLINDA, IDAC)** model has been configured and fitted for all organs, a `.cas` file for direct import into OLINDA or a `.idac` file for import into IDAC2.1 can be created as follows:

1. Select **Edit Data** from the **Tools** list in the lower right.

2. Switch the operation below the curve list to **Dosimetry OLINDA/EXM Export** or **Dosimetry IDAC Export**
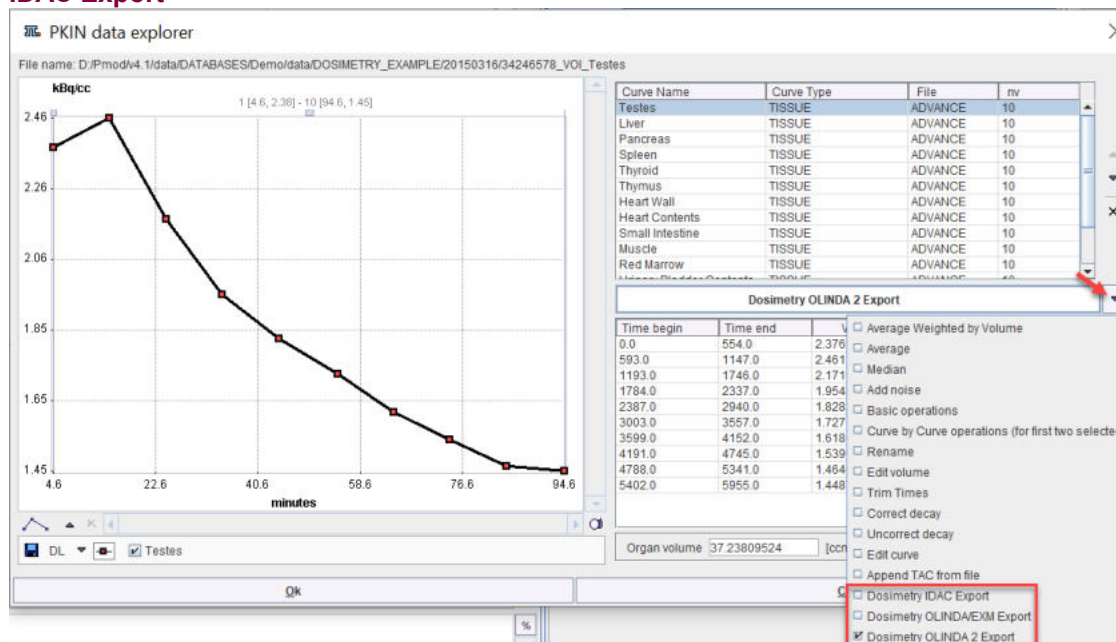
OLINDA/EXM Output

The appearing dialog window

lists the phantoms supported by OLINDA/EXM. Please select the appropriate one, but note that OLINDA/EXM doesn't interpret this information during loading of the `.cas` file. The option **Use default Olinda dose** should normally be on. Otherwise, the dose information in the patient SUV panel will be used which will most probably cause problems upon import, because OLINDA/EXM crashes when the dose values are not integer.

Finally specify a location and a name for saving the `.cas` file which can be loaded in OLINDA/EXM using the **Retrieve Case** button.
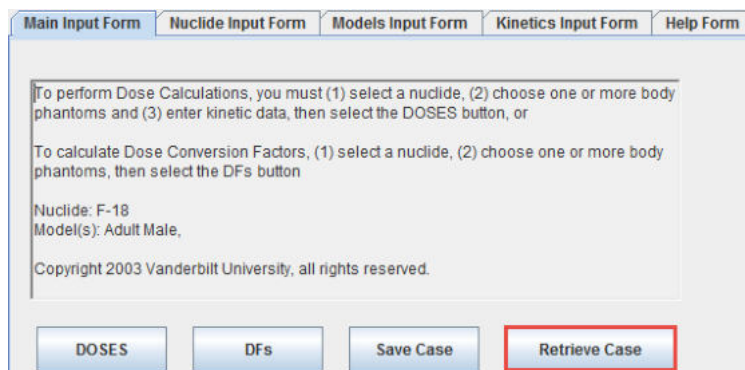
Note that the region names must be spelled exactly as below for the export/import to work properly.

> Adrenals
> Brain
> Breasts_including_skin
> Gallbladder_contents
> LLI_contents
> SI_contents
> Stomach_contents
> ULI_contents
> Heart_contents
> Heart_wall
> Kidneys
> Liver
> Lungs
> Muscle
> Ovaries
> Pancreas
> Red_marrow
> Cortical_bone
> Trabecular_bone
> Spleen
> Testes
> Thymus
> Thyroid
> Urinary_bladder_contents
> Uterus
> Fetus
> Placenta

The difference between the injected activity and the activity accumulated in all organs is treated as the Remainder.

OLINDA 2 Output

The appearing dialog window lists the phantoms supported by the export. Note that within OLINDA 2 the phantoms can be easily switched, whereby the activities are propagated.

Please select the appropriate one and save the file which is stored with `.cas` suffix. When opening the file in Olinda 2, the isotope and the model are selected, and the cumulated activities can be inspected on the **Set Kinetics** panel.

The **Remainder** value is automatically calculated from the total normalized number of disintegrations of the isotope (=Half-time[h]/ln(2)) minus the activity found in the organs (excluding the bladder). It shows up in the **Total Body/Remainder** field.
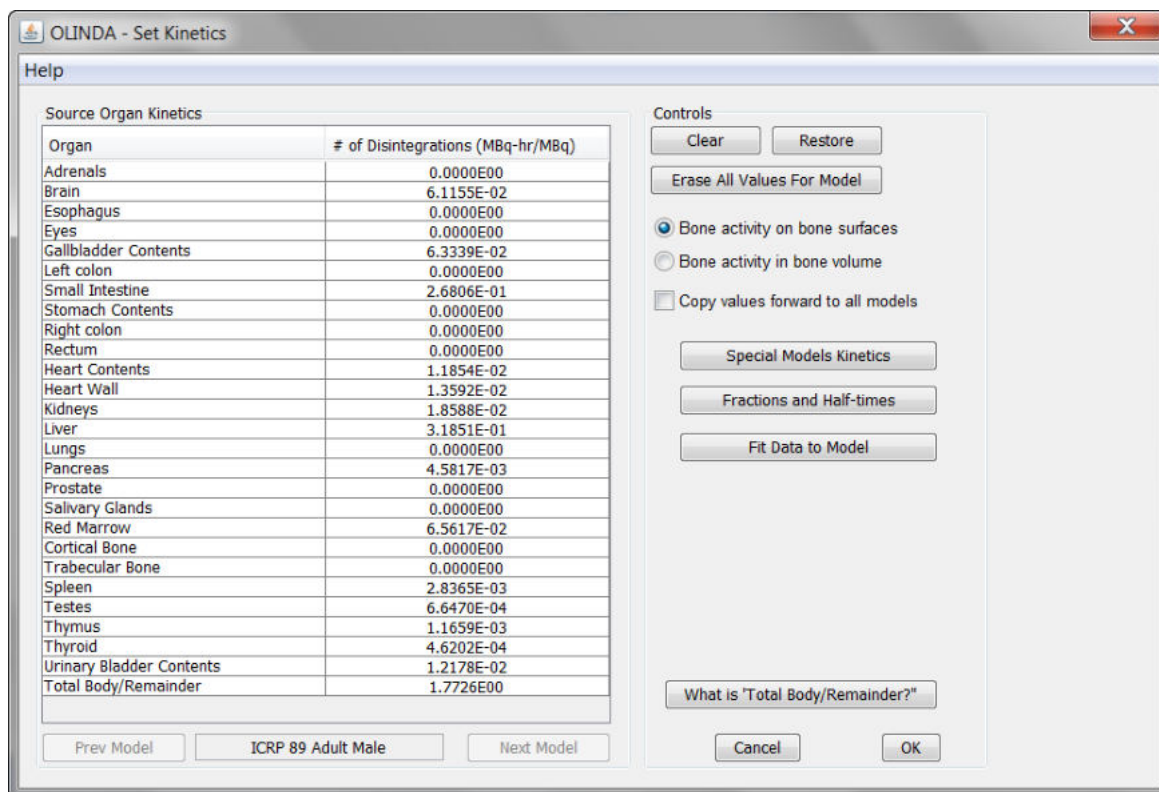
IDAC Output

The appearing dialog window
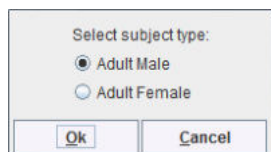
Please select the appropriate one and save the file which is stored with `.idac` suffix. When opening the file in IDAC2.1 the cumulated activity will be shown and available for calculating the doses.
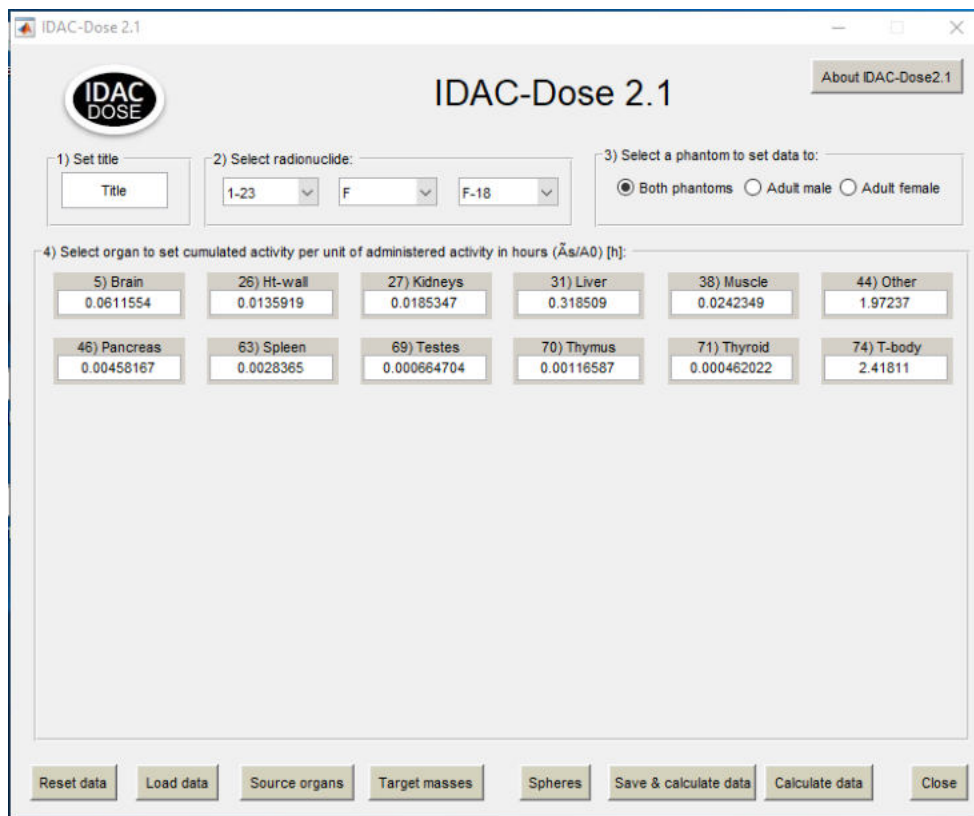
Note that the VOI names for the organs must be defined exactly as follows:

Female	Male
Adipose tissue	Adipose tissue
Adrenals	Adrenals
Alveolar-interstitial	Alveolar-interstitial
Brain	Brain
Breast	Breast
Bronchi basal cells	Bronchi basal cells
Bronchi secretory cells	Bronchi secretory cells
Bronchiolar secretory cells	Bronchiolar secretory cells
Endosteal cells	Endosteal cells
ET1 basal cells	ET1 basal cells
ET2 basal cells	ET2 basal cells
Extrathoracic lymph nodes	Extrathoracic lymph nodes
Gall bladder	Gall bladder
Heart wall	Heart wall
Kidneys	Kidneys
Left colon	Left colon
Lens of eye	Lens of eye
Liver	Liver
Muscle	Muscle
Oesophagus	Oesophagus
Oral mucosa	Oral mucosa
Ovaries	Pancreas
Pancreas	Pituitary gland
Pituitary gland	Prostate
Rectosigmoid colon	Rectosigmoid colon
Red (active) marrow	Red (active) marrow
Right colon	Right colon
Salivary glands	Salivary glands
Skin	Skin
Small intestine	Small intestine

Spleen	Spleen
Stomach	Stomach
Systemic lymph nodes	Systemic lymph nodes
Thoracic lymph nodes	Testes
Thymus	Thoracic lymph nodes
Thyroid	Thymus
Tongue	Thyroid
Tonsils	Tongue
Ureters	Tonsils
Urinary bladder	Ureters
Uterus	Urinary bladder
Total body (all activity)	Total body (all activity)

Use of Organ Lists for VOI Definition

The OLINDA and IDAC organ lists have been implemented in the VOI facility to support correct VOI naming. Illustrated below is use of these lists to assign proper name and organ mass to a defined VOI.
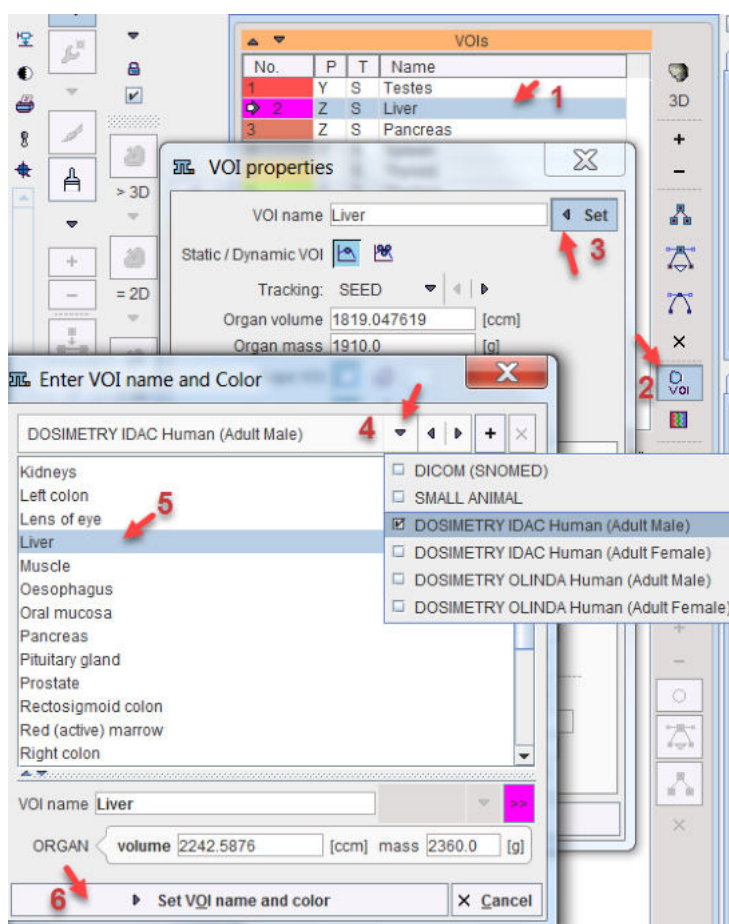
References

1. Stabin MG: Fundamentals of Nuclear Medicine Dosimetry. Springer; 2008. DOI

2. Stabin MG, Sparks RB, Crowe E: OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med 2005, 46(6):1023-1027.

6.5.13 Area under Curve (AUC)

This is an auxiliary model which cannot be used for fitting. It calculates the following curves from the input curve $C_P(t)$ and the selected regional tissue TAC $C_T(t)$ at the frame mid-times:

1. The AUC of the tissue TAC as a function of time:

$$AUC_T(t) = \int_0^t C_T(\tau)d\tau$$

2. The AUC of the input curve as a function of time:

$$AUC_P(t) = \int_0^t C_P(\tau)d\tau$$

   Note that the integration uses the interpolation model selected for the blood curves involved in the calculation of the input curve.

3. The ratio of the two AUCs as a function of time

$$AUC_{ratio}(t) = \int_0^t C_T(\tau)d\tau / \int_0^t C_P(\tau)d\tau$$

   It provides an indication of the tissue accumulation of the tracer [1].
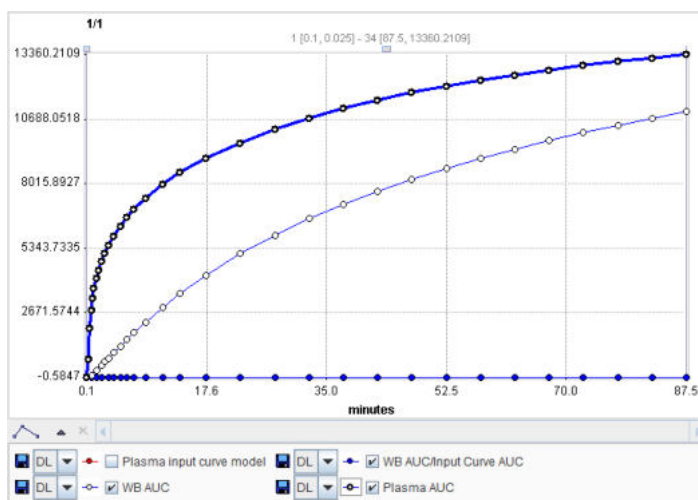
As the ratio curve has a completely different scaling than the curve integrals, it appears along the zero line. It can be shown with appropriate scaling by hiding all other curves. The easiest way to export the values is using the **Save all curves** or the **View values** option in the context menu (right click into curve area).

Reference

1. Eyal S, Chung FS, Muzi M, Link JM, Mankoff DA, Kaddoumi A, O'Sullivan F, Hebert MF, Unadkat JD: Simultaneous PET Imaging of P-Glycoprotein Inhibition in Multiple Tissues in the Pregnant Nonhuman Primate. Journal of Nuclear Medicine 2009, 50(5):798-806. DOI

6.5.14 Tissue/Plasma Ratio

This auxiliary model simply divides the tissue TAC at each frame mid-time by the interpolated plasma activity at the same time and displays it as a curve called **Tissue/Input curve Ratio**.
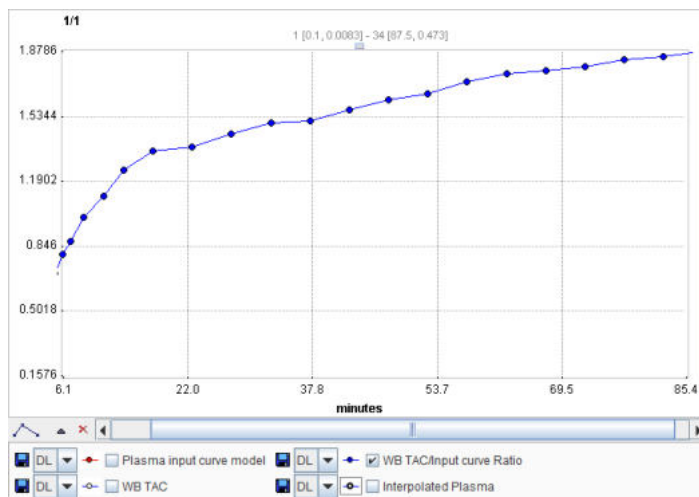
Under equilibrium conditions this ratio is equal to the total distribution volume of tracer in tissue. Therefore, the plot of the **Tissue/Input curve Ratio** against time is a quick means to check whether the system has equilibrated (plot becomes constant) or not.

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis as follows.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

6.5.15 Tissue Ratio Methods

This auxiliary model is aimed at receptor tracers for which a reference tissue without specific binding is available. It allows getting a quick estimate of the binding potential BP_{ND} using two different methods as described by Ito et al. [1].
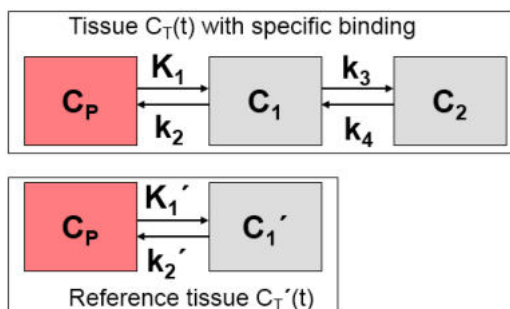
At the time, when specific binding C_2 peaks, its derivative equals zero (transient equilibrium) and $BP_{ND} = k_3/k_4 = C_2/C_1$ (non-specific/specific binding).

In practice, however, neither the C_1 part nor the C_2 part of a measured tissue TAC are known. As a pragmatic solution it is assumed that the non-displaceable compartment is equal among tissues, so the $C_T{}'(t)$ of reference tissue without specific binding is regarded as C_1, and C_2 is calculated by $C_T(t)-C_T{}'(t)$.

Operational Model Curve

Two different ratios are calculated by the **Tissue Ratio Methods** model:

$$BP_{ND} = \frac{k_3}{k_4} = \frac{C_2(t_{trans.equ.})}{C_1(t_{trans.equ.})} \simeq \frac{C_T(t_{trans.equ.}) - C_T{}'(t_{trans.equ.})}{C_T{}'(t_{trans.equ.})}$$

This ratio is calculated for all times, but it is *only valid at the time of transient equilibrium*. There is no automatic routine for detecting this peak. Rather, the user has to find this time by looking at the difference curve (enable check box).
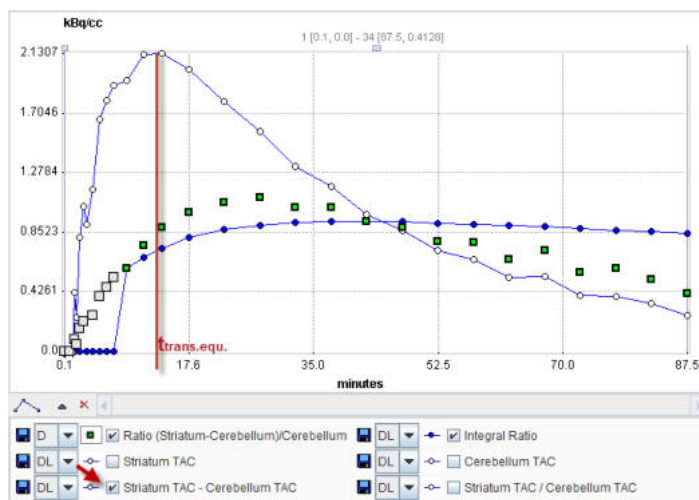
The second ratio calculated is called the *interval method* in [1].

$$BP_{ND} = \frac{k_3}{k_4} = \frac{\int\limits_{tb}^{te} C_2(t)dt}{\int\limits_{tb}^{te} C_1(t)dt}$$

Here, the two curves are integrated in a time interval $[t_b, t_e]$ which must include the time of transient equilibrium (t_b=9min. t_e=45 min for raclopride, where the time of transient equilibrium is in the range 20 to 24 min [1]).

Implementation

1. After switching to **Tissue Ratio Methods** a suitable reference tissue without specific binding must be selected.

2. The integration start time of the interval method must be specified by the user as the input parameter **Integral start time**.

3. The ratios are calculated for all times (for the integral method only after the **Integral start time**) and presented as curves. These curves can easily be exported as values using the save button 28 .

Reference

1. Ito H, Hietala J, Blomqvist G, Halldin C, Farde L: Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [11C]raclopride binding. J Cereb Blood Flow Metab 1998, 18(9):941-950. DOI

6.5.16 Tracer Retention Fraction

The *Retention Fraction* is the fraction of the total tracer delivered to an organ that is extracted into and retained by the tissue. It is the residual after clearances of the vascular component and the portion of the tracer that rapidly back diffuses from tissue to blood. Usually this fraction of tracer is sequestered in more slowly turning over metabolic or membrane binding processes. [1]

Operational Equation

Given a tissue TAC $C_T(t)$ and the input curve $C_P(t)$ this auxiliary model allows calculating the retention fraction R by [2]:

$$R = \frac{\int\limits_{t_b}^{t_e} C_T(\tau)d\tau}{\int\limits_{0}^{t_e} C_P(\tau)d\tau}$$

The denominator with the input curve integrated from the time of injection represents the available tracer, the numerator with the integral of the late tissue uptake the actually extracted tracer. Other authors [3] have used a simplified version of tracer retention which is calculated by dividing the tracer concentration by the input curve integral.

Note that an explicit blood volume correction is available via the **vB** input parameter. In the case of vB=0 (default setting), no correction is performed. For vB>0, the tissue TAC is corrected by the scaled whole blood activity before the actual analysis as follows.

$$C_T(t) = \frac{C_{PET}(t) - vB\, C_B(t)}{1 - vB}$$

Implementation

The **Tracer Retention** auxiliary model has two input parameters **Start** and **End** for the specification of t_b and t_e in the integration formula above, respectively. The curve display shows the input curve interpolated at the frame mid-times. The result parameters are calculated in % and %/min for the two calculation methods:

R_window [%]	Retention of tracer in the time window (Tissue-Integral in window)/(Plasma-Integral from start)
R_wind_min [%/min]	Retention of tracer in the time window (Tissue-Average in window)/(Plasma-Integral from start)
R_last [%]	Retention of tracer in the last frame of the acquisition (Tissue-Integral in window)/(Plasma-Integral from start)
R_last_min [%/min]	Retention of tracer in the last frame of the acquisition (Tissue-Average in window)/(Plasma-Integral from start)

References

1. *see* Glossary in Phelps ME: PET : molecular imaging and its biological applications. New York: Springer; 2004.

2. Hutchins GD, Chen T, Carlson KA, Fain RL, Winkle W, Vavrek T, Mock BH, Zipes DP: PET imaging of oxidative metabolism abnormalities in sympathetically denervated canine myocardium. J Nucl Med 1999, 40(5):846-853.

3. Di Carli MF, Tobes MC, Mangner T, Levine AB, Muzik O, Chakroborty P, Levine TB: Effects of cardiac sympathetic innervation on coronary blood flow. The New England journal of medicine 1997, 336(17):1208-1215.

6.5.17 Fractal Dimension

The **Fractal Dimension** model measures the complexity of a 2-dimensional structure by calculating its box-counting dimension [1]. This concept has been applied in oncologic studies for assessing the heterogeneity of tissue kinetics [2].

Operational Equation

The idea is to subdivide the area under the tissue TAC into a number of square boxes and simply count the number of boxes containing some part of the structure. The mesh size is defined as s, so 1/s gives the number of segments in each of the 2 dimensions. For instance, specifying 1/s=5 therefore means a subdivision into 5*5=25 boxes.

The counting process is performed with increasing number of intervals up to the specified 1/s. Next, the data are plotted in a double-logarithmic way, namely log(N(s)) on the y axis and log(1/s) on the x-axis.
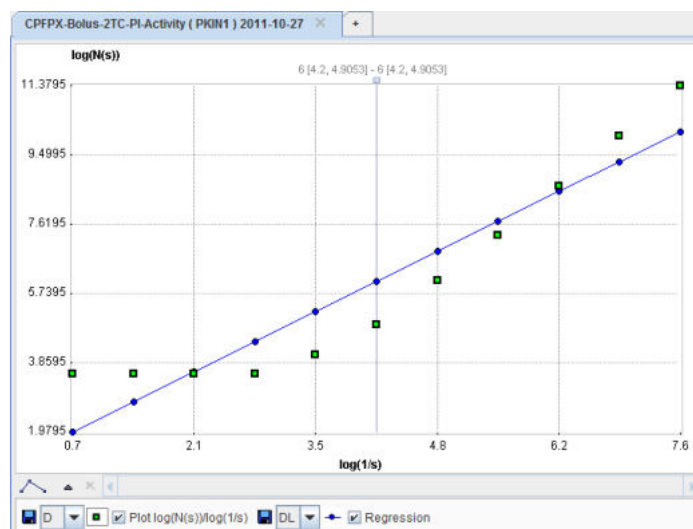
The box-counting dimension is finally obtained as the slope of a linear regression through the plotted points.

Implementation

After switching to the **Fractal dimension** model, two input parameters are available for specifying the box-counting process: **1/s**, and **Maximal value** the highest TAC value which might occur in the data.

References

1. Peitgen H-O, Jürgens H, Saupe D: Chaos and fractals : new frontiers of science. New York: Springer-Verlag; 1992.

2. Strauss LG, Dimitrakopoulou-Strauss A, Koczan D, Bernd L, Haberkorn U, Ewerbeck V, Thiesen HJ: 18F-FDG kinetics and gene expression in giant cell tumors. J Nucl Med 2004, 45(9):1528-1535.

6.6 Interpolation Functions for Whole-Blood and Plasma Activity

PKIN supports multiple functions which can be <u>fitted to measured blood activity data</u> 43 and allow interpolating intermediate values. Exceptions are the functions for the dispersion deconvolution, as described <u>above</u> 90.

6.6.1 Linear Activity Interpolation

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described <u>above</u> 41.

Operational Model Curve

The **Lin. Interpolation** model interpolates linearly between the measured activity values. Outside the measured values the following interpolation rules apply:

- If the first measurements occurs at t<0, the activity is assumed to be zero for all earlier times.

- If the first measurements occurs at t>0, the activity is assumed to be zero for t<=0. Activity values from t=0 up to the first measurement are calculated by linear interpolation from activity 0 at t=0.

- The activity is assumed to remain constant after the last measurement. For short blood curves it is therefore recommended to replace the tail of the measurements by a fitted tri-exponential [197] model.
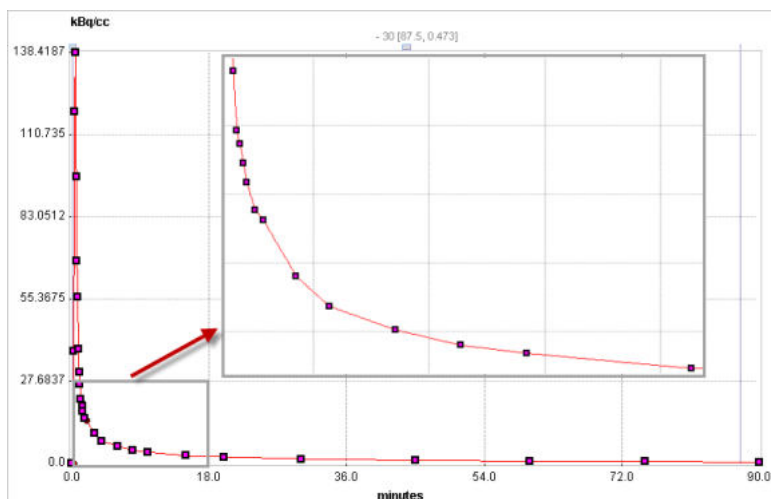
Parameter Fitting

The **Lin. Interpolation** model has no fitting parameter.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be fitted as an additional parameter [7] to the parameters of the kinetic model.

6.6.2 Decaying Exponentials

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described above [4].

Operational Model Curve

The **3 Exponentials** model allows replacing the tail of the blood activity curve by a fitted sum of up to three exponentials. The **Begin** parameter defines at what time the models switches from linear to tri-exponential interpolation. The exponentials are each defined by an **Amplitude** and a **Halftime** [min] of the decay. The number of exponentials can easily be reduced by fixing one or two of the amplitudes at a value of 0.

$$f_{Plasma/WB}(t) = \begin{cases} Lin.Interpol & t < Begin \\ \sum_{i=1}^{3} A_i \, e^{-u\ln 2/T_i} & t \geq Begin, u = t - Begin \end{cases}$$
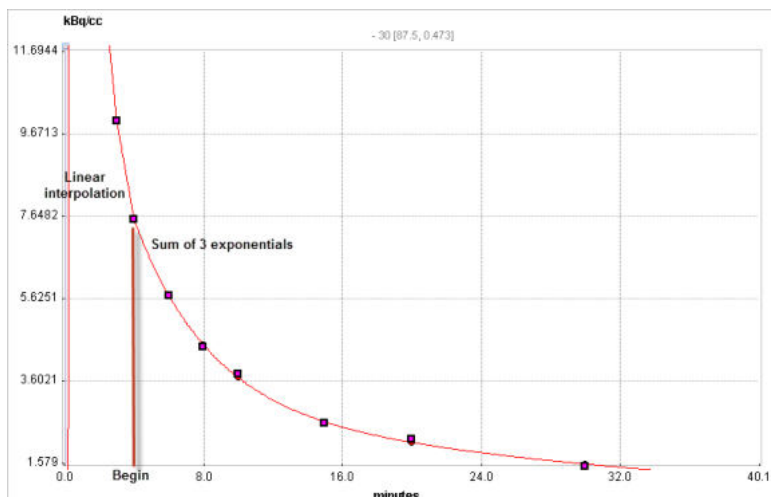
Parameter Fitting

Per default only two exponentials are enabled, and the **Begin** is initialized to the time of the blood peak. Use the **Fit plasma activity** or **Fit whole blood** button to fit the two exponentials to the measurements after the specified **Begin**. If the shape cannot be described well enough, enable the third exponential by enabling the fit boxes and set **Amplitude 3** to a positive number, then **Fit** again. Possibly, **Begin** has to be set to a later time for obtaining the signal tail.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be fitted as an additional parameter 7ħ to the parameters of the kinetic model.

6.6.3 Compartment Model with 3 Eigenvalues

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described above 4ħ.

Operational Model Curve

The **Compart, 3 EV** model has been developed for the FDG tracer [1]. It is the result from modeling the distribution and delivery of FDG in the circulatory system by a compartment model and results in an analytical solution with 3 eigenvalues (EV):

$$C_{continuous}(t) = \begin{cases} 0 & t < Begin \\ \left[A_1\, u - A_2 - A_3\right] e^{-u\ln 2/T_1} + A_2\, e^{-u\ln 2/T_2} + A_3\, e^{-u\ln 2/T3} & t \ge Begin,\, u = t - Begin \end{cases}$$
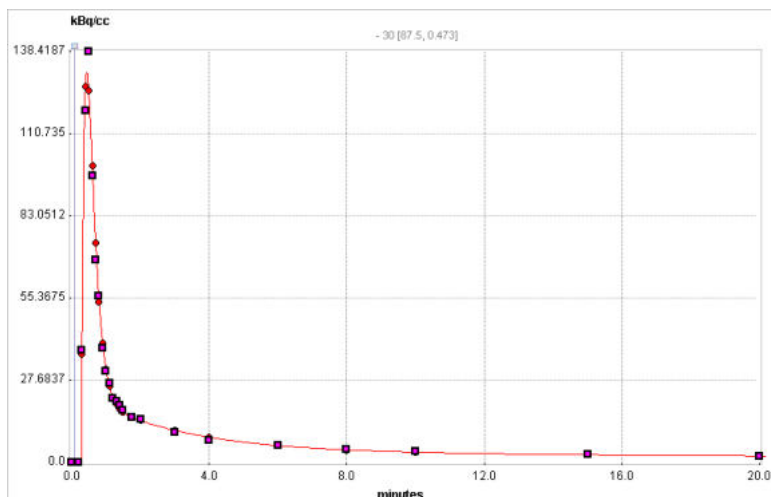
Parameter Fitting

Similar to the **3 Exponentials** model it includes a **Begin** parameter and three **Amplitude**s (A_1, A_2, A_3) and a **Halftime**s (T_1, T_2, T_3). However, the functional form supports a peak rising from time **Begin** followed by an exponentially decreasing tail. Use the **Fit plasma activity** or **Fit whole blood** button to fit the operational model curve to the measurements. Note that all samples are considered, not only the ones after **Begin**.

The form of the curve reacts very sensitively to changes of the parameters. The example above illustrates a peak which could not fully reach the maximum value. This model may be more suited for simulations rather than actual data processing.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be <u>fitted as an additional parameter</u> 7 to the parameters of the kinetic model.

Reference

1. Feng D, Huang SC, Wang X: Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography. International journal of bio-medical computing 1993, 32(2):95-110.

6.6.4   Compartment Model with 2 Eigenvalues

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described <u>above</u> 4 .

Operational Model Curve

The **Compart, 2 EV** model is an alternative model to the **Compart, 3 EV** model for the plasma activity curve of FDG [1]. It assumes repeated eigenvalues (EV) and has the following functional form:

$$C_{continuous}(t) = \begin{cases} 0 & t < Begin \\ [A_1 u - A_2] e^{-u \ln 2 / T_1} + A_2 e^{-u \ln 2 / T_2} & t \geq Begin, u = t - Begin \end{cases}$$
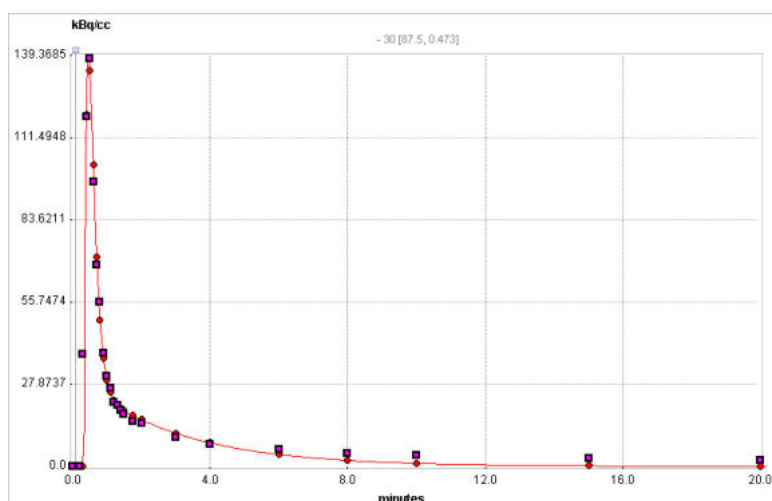
Parameter Fitting

Similar to the **3 Exponentials** model it includes a **Begin** parameter and two **Amplitude**s (A_1, A_2) and a **Halftime**s (T_1, T_2). However, the functional form supports a peak rising from time **Begin** followed by an exponentially decreasing tail. Use the **Fit plasma activity** or **Fit whole blood** button to fit the operational model curve to the measurements. Note that all samples are considered, not only the ones after **Begin**.

The form of the curve reacts very sensitively to changes of the parameters. The example above illustrates a result is model may be more suited for simulations rather than actual data processing.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be fitted as an additional parameter 7↑ to the parameters of the kinetic model.

Reference

1. Feng D, Huang SC, Wang X: Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography. International journal of bio-medical computing 1993, 32(2):95-110.

6.6.5   Gamma Function

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described above 4↑.

Operational Model Curve

The **Gamma Function** model is defined by the following functional form:

$$C_{continuous}(t) = \begin{cases} 0 & t < Begin \\ A\, u^B\, e^{-uC} & t \geq Begin, u = t - Begin \end{cases}$$

describing a sharp peak governed followed by a quick decay towards zero.
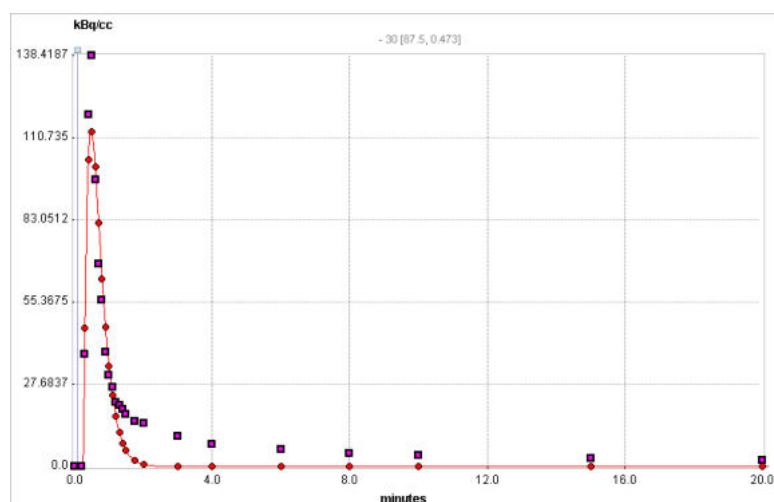
Parameter Fitting

The **Gamma Function** model includes a **Begin** time parameter for positioning the peak. The factor **A** scales the curve, the exponent **B** governs the rise and constant **C** the decay towards zero. Use the **Fit plasma activity** or **Fit whole blood** button to fit the operational model curve to the measurements. Note that all samples are considered, not only the ones after **Begin**.

The form of the curve reacts very sensitively to changes of the parameters. The example above illustrates the inability to fit model a peak followed by a moderate to slow decay appropriately. This model may therefore be more suited for simulations rather than actual data processing.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be fitted as an additional parameter 7↑ to the parameters of the kinetic model.

6.6.6 Gamma Function plus two Decaying Exponentials

The blood and plasma activity concentrations require interpolation procedures for kinetic modeling, as described above 4 .

Operational Model Curve

This **Gamma + 2 Exponentials** model is very similar to the Compartment Model with 3 Eigenvalues 198 . However, it includes a power term u^B which allows better modeling of sharp peaks.

$$C_{continuous}(t) = \begin{cases} 0 & t < Begin \\ \left[A_1 u^B - A_2 - A_3\right]e^{-u\ln 2/T_1} + A_2 e^{-u\ln 2/T_2} + A_3 e^{-u\ln 2/T3} & t \geq Begin, u = t - Begin \end{cases}$$
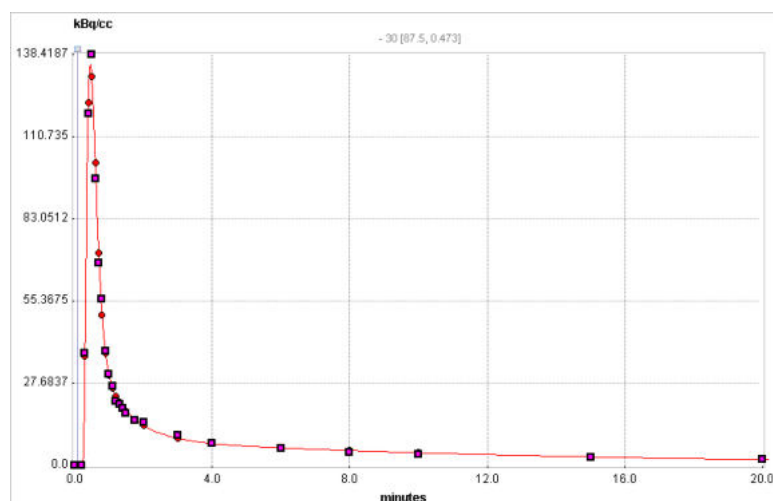
Parameter Fitting

The **Gamma + 2 Exponentials** model includes a **Begin** parameter, three **Amplitude**s (A_1, A_2, A_3) and a **Halftime**s (T_1, T_2, T_3), and a **Power Exponent** (B). This functional form supports a peak rising from time **Begin** followed by an exponentially decreasing tail. The initial default of the **Power Exponent** is a fixed value of 1 which corresponds to the **Compartment Model with 3 Eigenvalues**. Use the **Fit plasma activity** or **Fit whole blood** button to fit the operational model curve to the measurements. Then, for better fitting of the peak, enable the **Power Exponent** and fit again. The form of the curve reacts very sensitively to changes of the parameters. Note that all samples are considered, not only the ones after **Begin**.

The **Delay** parameter serves for correcting a timing offset between tissue and blood data. Positive delays correspond to delayed blood information and hence shift the blood curve to earlier times (to the left). The **Delay** is only relevant during the fitting of the tissue model where it can be fitted as an additional parameter 7 to the parameters of the kinetic model.

6.6.7 Simulation of Bolus/Infusion Tracer Application

When a compartment system has equilibrated, the total distribution volume can be calculated easily as the ratio of tracer concentration in tissue to the metabolite-corrected plasma concentration with a single static scan. It has been found that the time required to reach equilibrium can be shortened by an optimized tracer delivery. A setup which does not require a sophisticated tracer delivery system is to apply an initial bolus and continue with a constant infusion.

Carson et al. [1] have developed a method to optimize the ratio between the activity given as the initial bolus and the activity level of the subsequent infusion for quickly reaching an equilibrium (Appendix B in [1]). This method is implemented 18 as a tissue model in PKIN. The current blood model **Bolus/Infusion** is only a visualization model and should not be used for fitting measured blood data. It allows entering the K_{bol} value found with the tissue model optimization and inspecting the plasma activity curve under the bolus/infusion regime.

Operational Model Curve

For a bolus and infusion (B/I) experiment the expected input function can be derived from the input curve $C_P(t)$ of a bolus-only experiment by

$$C_{\text{Model}}(t) = \frac{K_{bol}C_P(t) + \int_0^t C_P(\tau)d\tau}{K_{bol} + T}$$

K_{bol} [min] defines the dose of the bolus expressed as minutes of infusion, and T is the total duration of the infusion (end of last frame).

Parameter Fitting

This model cannot be used for data fitting. It assumes the plasma activity curve of a bolus experiment has been loaded and visualizes the expected input curve if **Kbol** [min] equivalents of the infusion are applied as an initial bolus. The criterion of fast equilibration is that the model curve gets soon constant and remains so.

Reference

1. Carson RE, Channing MA, Blasberg RG, Dunn BB, Cohen RM, Rice KC, Herscovitch P: Comparison of bolus and infusion methods for receptor quantitation: application to [18F] cyclofoxy and positron emission tomography. J Cereb Blood Flow Metab 1993, 13(1):24-42. DOI

6.6.8 Flumazenil, HOT Input Curve

The **Multiinjection, HOT** model is used in combination with the tissue model for multi-injection studies with ^{11}C-Flumazenil as described by Delforge et al. [1]. Please refer to the documentation of the implemented tissue model 137 for a more detailed description.

It is assumed that the total plasma activity of the tracer $C_{\text{Plasma}}(t)$ is loaded from the menu as illustrated below.
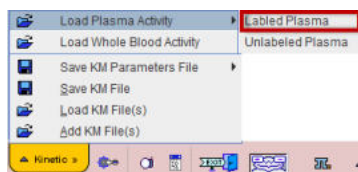
Operational Model Curve

The input curve is then calculated by applying an exponential metabolite correction which considers the two injections of hot ligand at time **T1** and **T3**:

$$C_P(t) = \begin{cases} C_{Plasma}\left(A_1 e^{B_1(t-T_1)} + A_2 e^{B_2(t-T_1)}\right) & T_1 < t < T_3 \quad \text{decay since 1}^{st}\text{ injection} \\ C_{Plasma}\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \quad \text{decay since 3}^{rd}\text{ injection} \end{cases}$$

Parameter Fitting

Note that although the corresponding parameters have a fit box, they should normally be used for entering pre-determined values of injection times and metabolite correction parameters. The default parameters of the for the bi-exponential metabolite correction (**A1**, **T1**, **A2**, **B2**) used in this model are from [1].

Reference

1. Delforge J, Pappata S, Millet P, Samson Y, Bendriem B, Jobert A, Crouzel C, Syrota A: Quantification of benzodiazepine receptors in human brain using PET, [11C]flumazenil, and a single-experiment protocol. J Cereb Blood Flow Metab 1995, 15(2):284-300. DOI

6.6.9 Flumazenil, COLD Input Curve

The **Multiinjection, COLD** model is used in combination with the tissue model for multi-injection studies with ^{11}C-Flumazenil as described by Delforge et al. [1]. Please refer to the documentation of the implemented tissue model [137] for a more detailed description.

It is assumed that the total plasma activity of the labeled tracer $C_{Plasma}(t)$ is loaded from the menu as illustrated below.
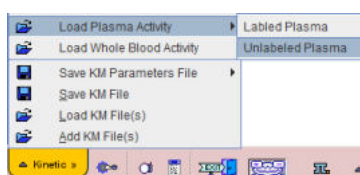
Operational Model Curve

The plasma activity of unlabeled (cold) ligand is calculated by using the information of the labeled (hot) ligand, scaling it proportionally to the applied dose, and applying the same metabolite correction. The metabolite corrected plasma activity of the labeled compound $C_P(t)$ is calculated by

$$C_P(t) = \begin{cases} C_{Plasma}\left(A_1 e^{B_1(t-T_1)} + A_2 e^{B_2(t-T_1)}\right) & T_1 < t < T_3 \quad \text{decay since 1}^{\text{st}} \text{ injection} \\ C_{Plasma}\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \quad \text{decay since 3}^{\text{rd}} \text{ injection} \end{cases}$$

The calculation of the plasma activity of the unlabeled ligand $C^u_P(t)$ is also performed differently in two time segments:

$$C^{u}{}_{P}(t) = \begin{cases} Dose_2 / Dose_1\, C_P(t - T_2) & T_2 < t < T_3 \\ Dose_3{}^{Cold} / Dose_3{}^{Hot}\, C_P(t - T_3) + C^{u}{}_{P}(T_3)\left(A_1 e^{B_1(t-T_3)} + A_2 e^{B_2(t-T_3)}\right) & t > T_3 \end{cases}$$

1. Following the cold-only injection at T_2 the input curve of the first hot injection at T_1 is scaled according to the dose ration and shifted to start at T_2.

2. Following the injection at T_3 with hot and cold ligand the input curve of the hot ligand is scaled, and a contribution of the first cold injection added which is decreasing by the metabolite build-up.
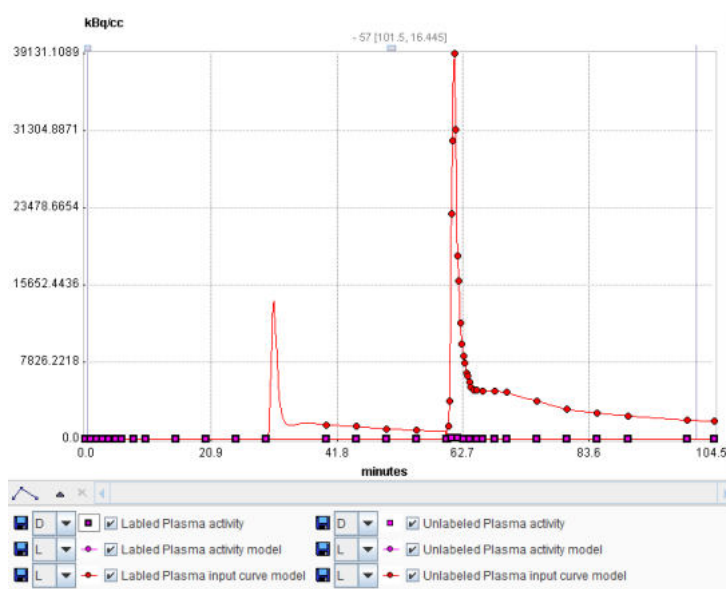
Parameter Fitting

Note that although the corresponding parameters have a fit box, they should normally be used for entering pre-determined values of injection times and metabolite correction parameters. The default parameters of the for the bi-exponential metabolite correction (**A1**, **T1**, **A2**, **B2**) used in this model are from [1].

Reference

1. Delforge J, Pappata S, Millet P, Samson Y, Bendriem B, Jobert A, Crouzel C, Syrota A: Quantification of benzodiazepine receptors in human brain using PET, [11C]flumazenil, and a single-experiment protocol. J Cereb Blood Flow Metab 1995, 15(2):284-300. DOI

6.6.10 Calibration: Step-Up

The purpose of this model is to determine dispersion parameters from a blood sampler calibration measurement, as explained in a specific section 93 .

6.6.11 Calibration: Step-Down

The purpose of this model is to determine dispersion parameters from a blood sampler calibration measurement, as explained in a specific section 93 .

6.6.12 Calibration: Correction

The purpose of this model is to apply dispersion parameters calculated from a blood sampler calibration measurement to the blood curve of a live experiment, as described in a specific section 95 .

6.7   Interpolation Functions for Plasma/Whole-Blood Fraction

The following functions for converting whole-blood activity into plasma activity are available in PKIN. Note that it is feasible to combine the conversion into plasma activity and then into authentic tracer activity into a single conversion function. In this case the parent fraction can remain the identity function, which is its default.

6.7.1   Fix Plasma Fraction

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section[4]. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a whole-blood activity curve has been loaded with **Load Whole Blood Activity** entry in the menu.
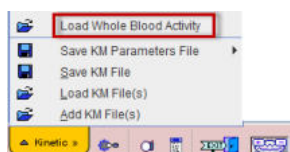
With the **Fix** model the activity concentration in plasma is assumed to be proportional to the activity concentration in whole blood. The proportionality constant **Fraction** has to be specified by the user and has a default of 1.

Note that as long as no other plasma-related data is loaded or the plasma fraction changed, the **Fix** model is applied so that the whole-blood activity curve will be used as the input curve.

Parameter Fitting

There is nothing to fit with the **Fix** model.

6.7.2   Linear Interpolation of Plasma/Whole-blood Fraction

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section[4]. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.


The **Lin. Interpolation** model interpolates linearly between the measured fraction values. Outside the measured values the following interpolation rules apply:

- The fraction at time t=0 is assumed to equal 1.
- The fraction is assumed to remain constant after the last measured fraction.

For incomplete fraction data it is therefore recommended to replace the tail of the measurements by a fitted tri-exponential[206] model.
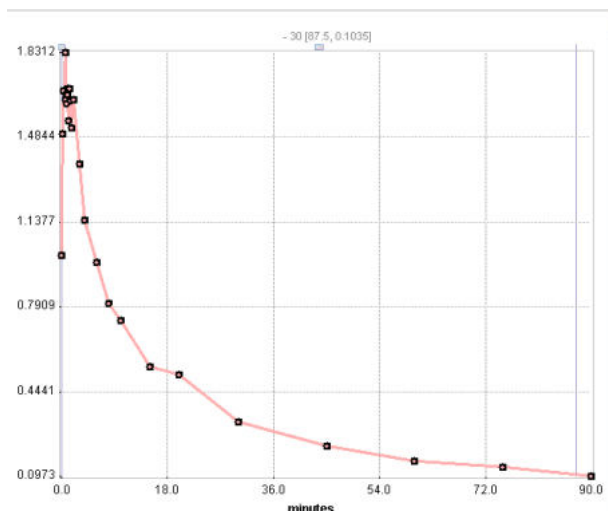
Parameter Fitting

There is nothing to fit with the **Lin. Interpolation** model.

6.7.3 Exponential Plasma/Whole-blood Fraction

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.


Operational Model Curve

The **3 Exponentials** model allows replacing the tail of the fraction curve by a fitted sum of up to three exponentials. The **Begin** parameter defines at what time the models switches from linear to tri-exponential interpolation. The exponentials are each defined by an **Amplitude** and a **Halftime** [min] of the decay. The number of exponentials can easily be reduced by fixing one or two of the amplitudes at a value of 0.

$$f_{Plasma/WB}(t) = \begin{cases} Lin.Interpol & t < Begin \\ \sum_{i=1}^{3} A_i \, e^{-u \ln 2 / T_i} & t \geq Begin, u = t - Begin \end{cases}$$

The illustration below shows an example with the exponentials fitted following 2 minutes (**Begin** = 120sec). Note that the linear interpolation assumes a fraction of 1 at t=0.
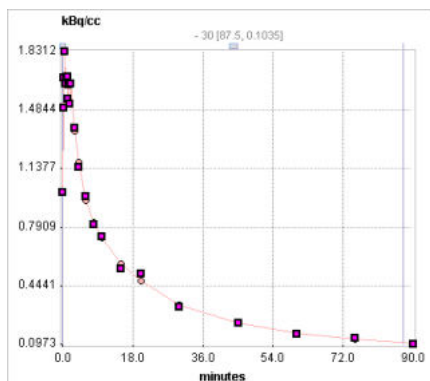
Parameter Fitting

The model supports the fitting of the parameters **Begin**, **Amplitude 1**, **2**, **3** (=A_1, A_2, A_3) and **Halftime 1**, **2**, **3** (=T_1, T_2, T_3). Fitting is started with the **Fit plasma fraction** button, which only takes the samples after the **Begin** time into consideration.

Appropriate default parameters for FDG scans:

- Rat experiments [1]: Plasma/whole_blood(t) = $0.51\,e^{(-\ln2/4.79\,t)}+0.3\,e^{(-\ln2/337\,t)}+0.8$
- Mouse Experiments [2]: Plasma/whole_blood(t) = $0.386*e_{(-0.191*t)}+1.165$

Use without Measured Fraction

If no measured plasma/whole-blood fraction data is available, the **3 Exponentials** model can still be applied. In this case the **Begin** time is disregarded, and the functional defined by the entered parameters applied.
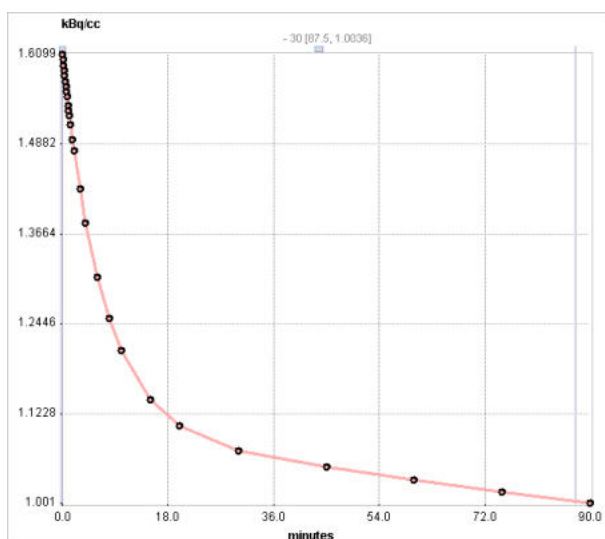

References

1. Weber B, Burger C, Biro P, Buck A: A femoral arteriovenous shunt facilitates arterial whole blood sampling in animals. Eur J Nucl Med Mol Imaging 2002, 29(3):319-323.

2. Ferl GZ, Zhang X, Wu HM, Kreissl MC, Huang SC: Estimation of the 18F-FDG input function in mice by use of dynamic small-animal PET and minimal blood sample data. J Nucl Med 2007, 48(12):2037-2045. [DOI](#)

6.7.4 Hill Function

The sequential steps for converting blood measurements to an input curve are explained in a [dedicated section](#) 41. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.
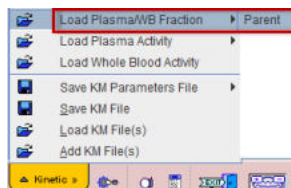
Operational Model Curve

The **Hill** model allows replacing the tail of the fraction curve by an analytical function. The **Begin** parameter defines at what time the models switches from linear interpolation to the Hill function.

$$f_{Plasma/WB}(t) = \begin{cases} Lin.Interpol & t \leq Begin \\ scale \cdot \left[1 - \left(\dfrac{A\,u^B}{u^B + C} \right) \right] & t > Begin,\, u = t - Begin \end{cases}$$

The illustration below shows an example with the Hill function fitted following 2 minutes (**Begin** = 120sec). The the weighting has been changed for putting more emphasis on the tail. Note that the linear interpolation assumes a fraction of 1 at t=0.
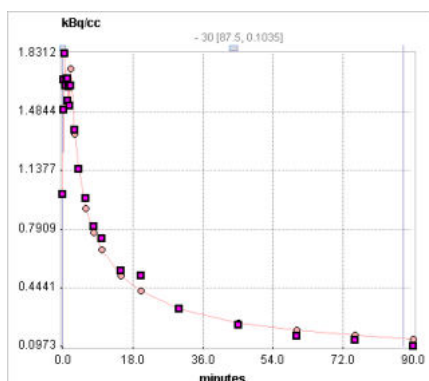
Parameter Fitting

The model supports the fitting of the parameters **Begin**, **scale**, **A**, **B**, **C.** Fitting is started with the **Fit plasma fraction** button, which only takes the samples after the **Begin** time into consideration.

Use without Measured Fraction

If no measured plasma/whole-blood fraction data is available, the **Hill** model can still be applied. In this case the **Begin** time is disregarded, and the functional defined by the entered parameters applied.

References

1. Gunn RN, Sargent PA, Bench CJ, Rabiner EA, Osman S, Pike VW, Hume SP, Grasby PM, Lammertsma AA: Tracer kinetic modeling of the 5-HT1A receptor ligand [carbonyl-11C]WAY-100635 for PET. Neuroimage 1998, 8(4):426-440. DOI

6.7.5 Watabe Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.
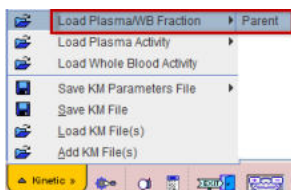
Operational Model Curve

The **Watabe** model allows replacing the tail of the fraction curve by an analytical function. The **Begin** parameter defines at what time the models switches from linear interpolation to the Hill function.

$$f_{Plasma/WB}(t) = \begin{cases} Lin.Interpol & t \le Begin \\ \dfrac{scale}{\left[1+(Au)^B\right]^C} & t > Begin, u = t - Begin \end{cases}$$

The illustration below shows an example with the Hill function fitted following 2 minutes (**Begin** = 120sec). The the weighting has been changed for putting more emphasis on the tail. Note that the linear interpolation assumes a fraction of 1 at t=0.
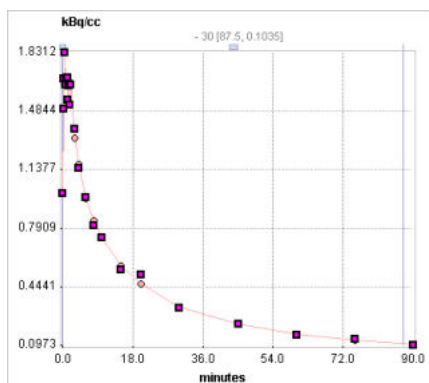
Parameter Fitting

The model supports the fitting of the parameters **Begin**, **scale**, **A**, **B**, **C.** Fitting is started with the **Fit plasma fraction** button, which only takes the samples after the **Begin** time into consideration.

Use without Measured Fraction

If no measured plasma/whole-blood fraction data is available, the **Watabe** model can still be applied. In this case the **Begin** time is disregarded, and the functional defined by the entered parameters applied.

References

1. Watabe H, Channing MA, Der MG, Adams HR, Jagoda E, Herscovitch P, Eckelman WC, Carson RE: Kinetic analysis of the 5-HT2A ligand [11C]MDL 100,907. J Cereb Blood Flow Metab 2000, 20(6):899-909. DOI

6.7.6　Sigmoid Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.
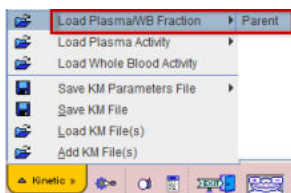
Operational Model Curve

The **Sigmoid** model allows replacing the tail of the fraction curve by an analytical function. The **Begin** parameter defines at what time the models switches from linear interpolation to the Hill function.

$$f_{Plasma/WB}(t) = \begin{cases} Lin.Interpol & t \leq Begin \\ scale \cdot \left[\left(1 - \dfrac{u^3}{u^3 + 10^A}\right)^B + C \right] / (1 + C) & t > Begin, u = t - Begin \end{cases}$$

The illustration below shows an example with the Hill function fitted following 2 minutes (**Begin** = 120sec). The the weighting has been changed for putting more emphasis on the tail. Note that the linear interpolation assumes a fraction of 1 at t=0.
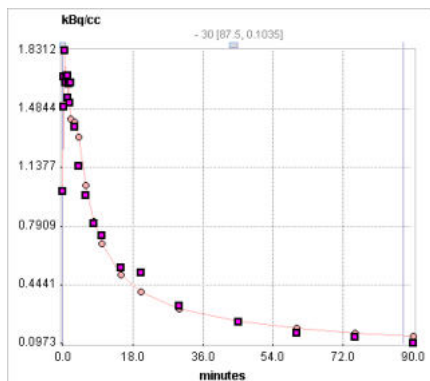
Parameter Fitting

The model supports the fitting of the parameters **Begin**, **scale**, **A**, **B**, **C.** Fitting is started with the **Fit plasma fraction** button, which only takes the samples after the **Begin** time into consideration.

Use without Measured Fraction

If no measured plasma/whole-blood fraction data is available, the **Sigmoid** model can still be applied. In this case the **Begin** time is disregarded, and the functional defined by the entered parameters applied.

References

1. Owen DR, Guo Q, Kalk NJ, Colasanti A, Kalogiannopoulou D, Dimber R, Lewis YL, Libri V, Barletta J, Ramada-Magalhaes J, Kamalakaran A, Nutt DJ, Passchier J, Matthews PM, Gunn RN, Rabiner EA. Determination of [(11)C]PBR28 binding potential in vivo: a first human TSPO blocking study. J Cereb Blood Flow Metab. 2014;34(6):989-94. DOI

6.7.7 Linear Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current plasma fraction model serves for converting a whole-blood activity curve into a plasma-activity curve.

It is assumed that a curve representing the measured fractions of plasma/whole-blood activity has been loaded with **Load Plasma/WB Fraction**.
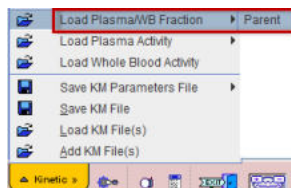
The **Linear** model provides a linear function with **Slope** and **Intercept** parameters which can be fitted to the plasma fraction values.

6.8 Interpolation Functions for Parent/Plasma Fraction

The following parent fraction models are available in PKIN.

6.8.1 Fix Parent/Plasma Fraction

The sequential steps for converting blood measurements to an input curve are explained in a [dedicated section][41]. The current [parent fraction][46] model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

Operational Model Curve

The **Fix** model assumes that the concentration of authentic tracer in plasma is in constant proportion to the concentration of total tracer in plasma. The fraction $f_{parent}(t)$ of authentic tracer to total tracer in plasma is therefore given by

$$f_{parent}(t) = f_p$$

with f_p representing the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

> **Note:** The **Fix** model is the default as soon as blood data is loaded. This is adquate if a metabolite correction is not necessary or has been performed in a prior step, for instance externally before loading the plasma activity.
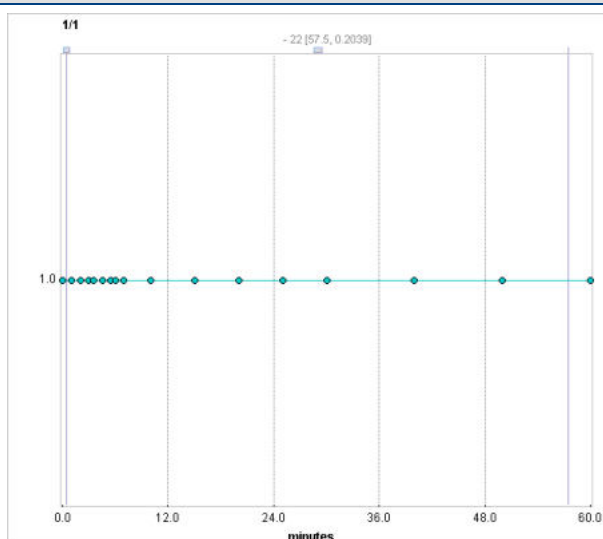
Parameter Fitting

There is nothing to fit with the **Lin. Interpolation** model. The only input parameter is the free fraction **fp** which defaults to 1, as it is experimentally difficult to measure.

6.8.2 Linear Interpolation Fraction

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section [41]. The current parent fraction [46] model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **Lin. Interpolation** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
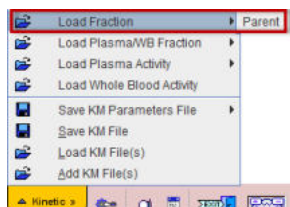

Operational Model Curve

The **Lin. Interpolation** model interpolates linearly between the measured fraction values F_k.

$$f_{parent}(t) = f_p \cdot Interpol(F_k)$$

and multiplies with f_p representing the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

Outside the measured values the following interpolation rules apply:

- The fraction at time t=0 is assumed to equal 1.
- The fraction is assumed to remain constant after the last measured fraction. For incomplete fraction data it is therefore recommended to replace the tail of the measurements by a fitted tri-exponential [215] model.

Note that fraction values >1 are not allowed.
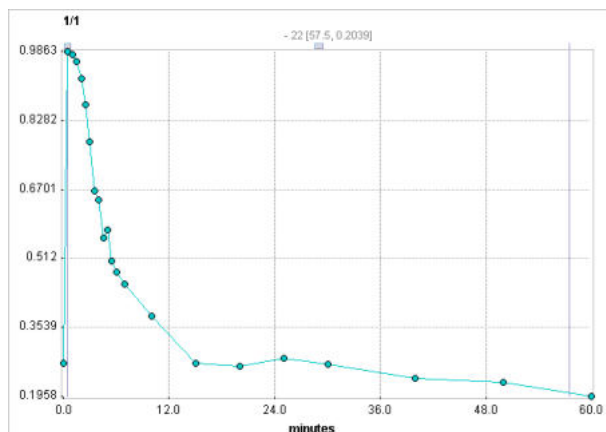
Parameter Fitting

There is nothing to fit with the **Lin. Interpolation** model. The only input parameter is the free fraction **fp** which defaults to 1, as it is experimentally difficult to measure.

6.8.3 1-Exponential

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section [41]. The current parent fraction [46] model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **1-Exponential** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
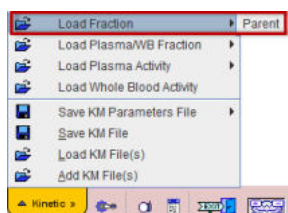
Operational Model Curve

The **1-Exponential** model applied by Wu et al [1] for modeling of the parent fraction has the following functional form

$$
f_{parent}(t) = f_p \cdot \begin{cases} 1 & t \leq Begin \\ Ae^{-u\ln 2/T} + (1-A) & t > Begin, u = t - Begin \end{cases}
$$

The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

The fraction calculation assumes negligible metabolites before a **Begin** time, and therefore remains constant at 1. From **Begin** on it decreases exponentially towards an equilibration fraction (1-A) with halftime T.
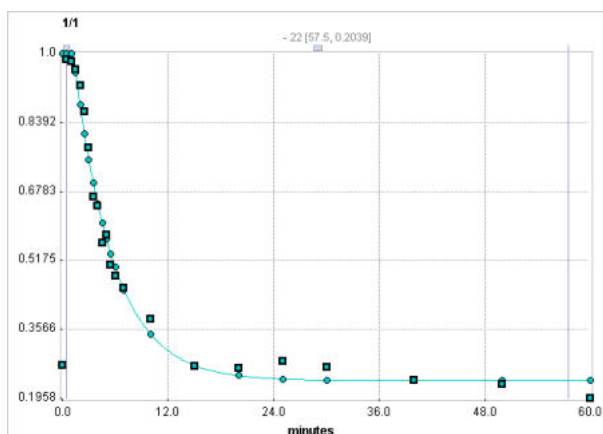
Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **Begin**, **Scale** (=A) and **Halftime.** All data samples are considered in the fitting process irrespective of **Begin**. The **Scale** parameter is restricted to the range [0,1] per default.
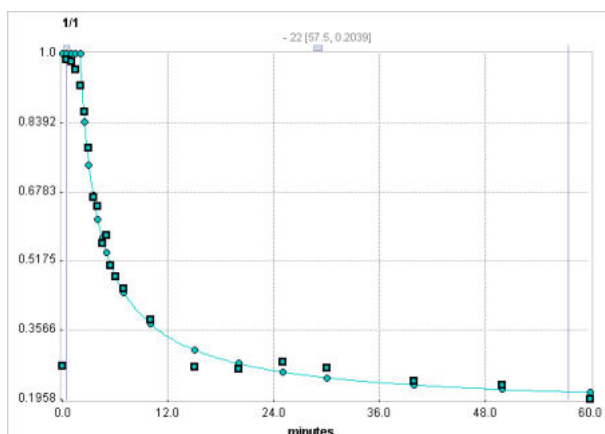
Use without Measured Parent Fraction

The **1-Exponential** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

Reference

1. Wu S, Ogden RT, Mann JJ, Parsey RV: Optimal metabolite curve fitting for kinetic modeling of 11C-WAY-100635. J Nucl Med 2007, 48(6):926-931. DOI

6.8.4   2-Exponentials

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **2-Exponential** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.

Operational Model Curve

The **2-Exponential** model applied by Wu et al [1] for modeling of the parent fraction has the following functional form

$$f_{parent}(t) \quad = \quad f_p \cdot \begin{cases} 1 & t \le Begin \\ Ae^{-u\ln 2/T_1} + (1-A)e^{-u\ln 2/T_2} & t > Begin, u = t - Begin \end{cases}$$

The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

The fraction calculation assumes negligible metabolites before a **Begin** time, and therefore remains constant at 1. From **Begin** on it decreases as a sum of two exponentials with halftimes T_1 and T_2. Note that because only one scale factor A is used, continuity at time **Begin** is ensured.
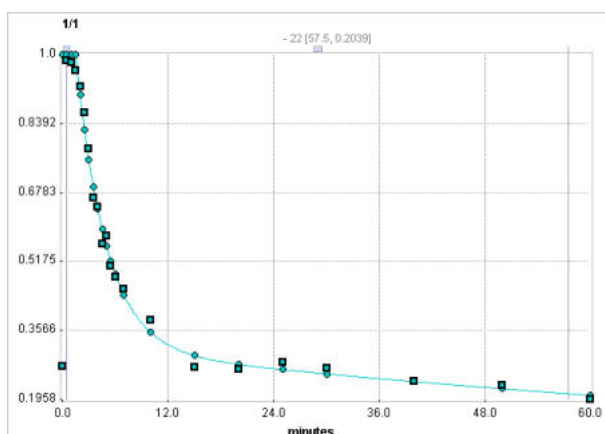
Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **Begin**, **Scale** (=A), **Halftime 1** and **Halftime 2.** All data samples are considered in the fitting process irrespective of **Begin**. The **Scale** parameter is restricted to the range [0,1] per default.

Use without Measured Parent Fraction

The **2-Exponential** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.
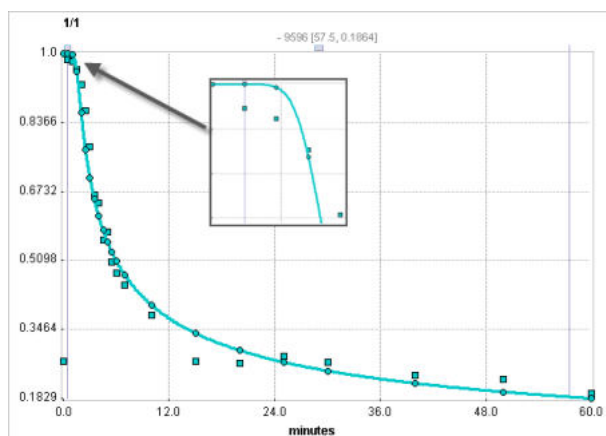
Reference

1. Wu S, Ogden RT, Mann JJ, Parsey RV: Optimal metabolite curve fitting for kinetic modeling of 11C-WAY-100635. J Nucl Med 2007, 48(6):926-931. DOI

6.8.5   3-Exponentials

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **3-Exponential** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
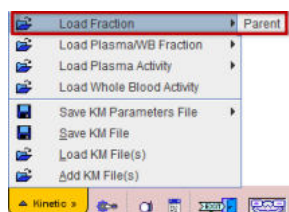

Operational Model Curve

The general **3-Exponential** model for the parent fraction has the following functional form

$$f_{parent}(t) \;=\; f_p \cdot \begin{cases} 1 & t \le Begin \\ A_1\, e^{-u\ln 2/T_1} + A_2\, e^{-u\ln 2/T_2} + A_3\, e^{-u\ln 2/T_3} & t > Begin,\, u = t - Begin \end{cases}$$

The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

The fraction calculation assumes negligible metabolites before a **Begin** time, and therefore remains constant at 1. From **Begin** on it decreases as a sum of three exponentials with halftimes T_1, T_2 and T_3. Note that the calculated fractions are restricted to the physiologic [0,1] value range.
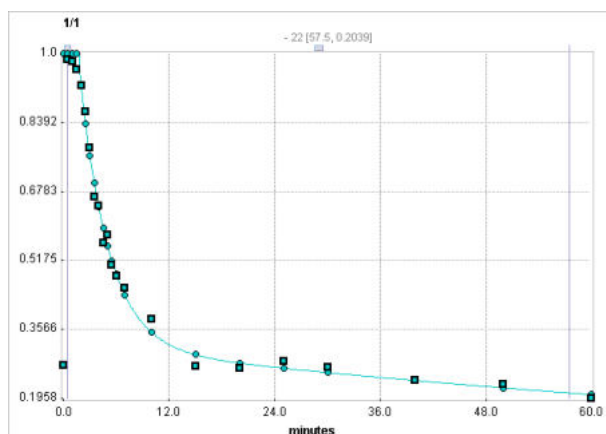
Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **Begin**, **Amplitude 1**, **2**, **3** (=A_1, A_2, A_3) and **Halftime 1**, **2**, **3** (=T_1, T_2, T_3). All data samples are considered in the fitting process irrespective of **Begin**. The three **Amplitude** parameters are restricted to the range [0,1] per default.

Use without Measured Parent Fraction

The **3-Exponential** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

6.8.6 Hill Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **Hill** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
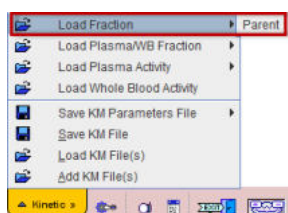

Operational Model Curve

The **Hill** model applied by Gunn et al [1] for modeling of the parent fraction has the following functional form

$$
f_{parent}(t) = f_p \cdot \begin{cases} 1 & t \leq Begin \\ 1 - \left(\dfrac{Au^B}{u^B + C} \right) & t > Begin, u = t - Begin \end{cases}
$$

whereby the calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

The fraction calculation assumes negligible metabolites before a **Begin** time, and therefore remains constant at 1. From **Begin** on it decreases smoothly.

Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the **Hill** curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **Begin**, **A**, **B** and **C.** All data samples are considered in the fitting process irrespective of **Begin**. The scaling parameter **A** is restricted to the range [0,1] per default.

Use without Measured Parent Fraction

The **Hill** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

Reference

1. Gunn RN, Sargent PA, Bench CJ, Rabiner EA, Osman S, Pike VW, Hume SP, Grasby PM, Lammertsma AA: Tracer kinetic modeling of the 5-HT1A receptor ligand [carbonyl-11C]WAY-100635 for PET. Neuroimage 1998, 8(4):426-440. DOI

6.8.7 Watabe Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **Watabe** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
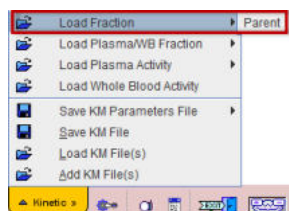
Operational Model Curve

The **Watabe** model applied by Watabe et al [1] for modeling of the parent fraction has the following functional form

$$f_{parent}(t) = f_p \cdot \left\{ \begin{array}{ll} 1 & t \leq Begin \\ \dfrac{1}{\left[1 + \{Au\}^B\right]^C} & t > Begin, u = t - Begin \end{array} \right\}$$

with **B** set to 2. The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.

The fraction calculation assumes negligible metabolites before a **Begin** time, and therefore remains constant at 1. From **Begin** on it decreases smoothly.

Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **Begin**, **A**, **B** and **C.** All data samples are considered in the fitting process irrespective of **Begin**. The scaling parameter **A** is restricted to the range [0,1] per default.

Use without Measured Parent Fraction

The **Watabe** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

Reference

1. Watabe H, Channing MA, Der MG, Adams HR, Jagoda E, Herscovitch P, Eckelman WC, Carson RE: Kinetic analysis of the 5-HT2A ligand [11C]MDL 100,907. J Cereb Blood Flow Metab 2000, 20(6):899-909. DOI

6.8.8   Power-Damped Exponentials

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **Power-Damped Exp** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
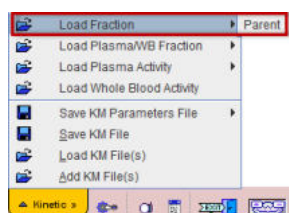
Operational Model Curve

The general **Power-Damped Exp** model for the parent fraction handles the situation where the parent fraction starts at a low value and then increases, before dropping. It has the following functional form

$$f_{parent}(t) = f_p \cdot \begin{cases} 0 & t \le 0 \\ t^{\alpha} \left(A_1 e^{-t \ln 2/T_1} + A_2 e^{-t \ln 2/T_2} + A_3 e^{-t \ln 2/T_3} \right) & t > 0 \end{cases}$$

The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.
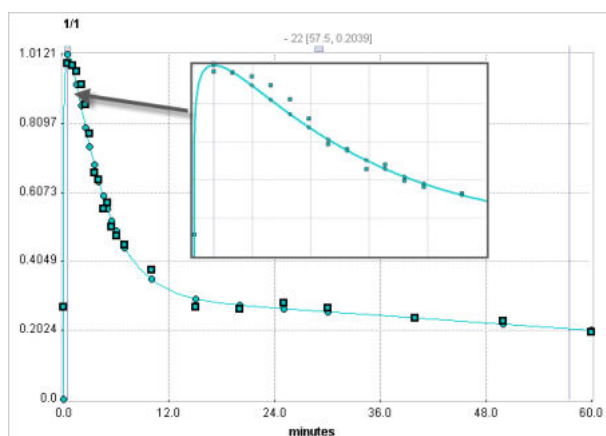
Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure.

The model supports the fitting of the parameters **alpha**, **Amplitude 1**, **2**, **3** (=A_1, A_2, A_3) and **Halftime 1**, **2**, **3** (=T_1, T_2, T_3). The three **Amplitude** parameters are restricted to the range [0,1] per default. However, the calculated fractions are *not* restricted to a certain value range.

Use without Measured Parent Fraction

The **Power-Damped Exp** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

Reference

1. Parsey RV, Ojha A, Ogden RT, Erlandsson K, Kumar D, Landgrebe M, Van Heertum R, Mann JJ: Metabolite considerations in the in vivo quantification of serotonin transporters using 11C-DASB and PET in humans. J Nucl Med 2006, 47(11):1796-1802. PDF

6.8.9   Sigmoid Function

The sequential steps for converting blood measurements to an input curve are explained in a dedicated section 41. The current parent fraction 46 model serves for converting a plasma activity curve into an input curve (authentic, unchanged tracer in plasma).

The **Sigmoid** model assumes that the concentration ratio of authentic tracer to total tracer in plasma has been determined at certain times during the acquisition and loaded with the **Load Fraction** entry in the menu.
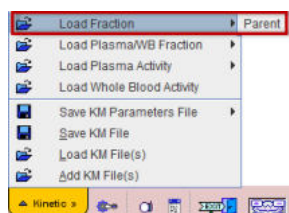
Operational Model Curve

The general **Sigmoid** function for the parent fraction has been applied for [11C]PBR28 and has the following functional form [1]

$$f_{parent}(t) = f_p \cdot \left\{ \begin{array}{ll} 1 & t \le Begin \\ \left(\left(1 - \dfrac{u^3}{u^3 + 10^A} \right)^B + C \right) / (1 + C) & t > Begin, u = t - Begin \end{array} \right\}$$

The calculated fraction is multiplied with f_p, the free fraction of authentic tracer in plasma, i.e. the fraction of tracer not bound to plasma proteins.
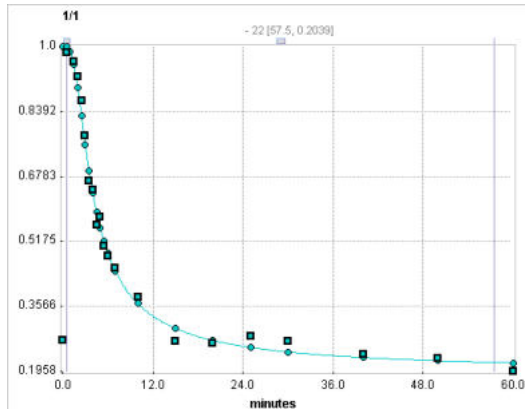
Parameter Fitting

The free fraction **fp** is an input parameter which has no impact on fitting the model curve to the fraction data. The default for **fp** is 1 as it is experimentally difficult to measure. The model supports the fitting of the parameters **A**, **B** and **C**.

Use without Measured Parent Fraction

The **Sigmoid** parent fraction model can be applied even if no parent fraction measurements were loaded. In this case the user has to specify a parameter set which establishes a representative metabolite correction for the used tracer.

Reference

1. Owen DR, Guo Q, Kalk NJ, Colasanti A, Kalogiannopoulou D, Dimber R, Lewis YL, Libri V, Barletta J, Ramada-Magalhaes J, Kamalakaran A, Nutt DJ, Passchier J, Matthews PM, Gunn RN, Rabiner EA. Determination of [(11)C]PBR28 binding potential in vivo: a first human TSPO blocking study. J Cereb Blood Flow Metab. 2014;34(6):989-94. DOI

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